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THERAPY PHYSICS BIOLOGY

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Vol. 6 Fasc 1 | THERAPY PHYSICS BIOLOGY | 1967 February

SURVIVAL RATES FOR UTERINE CANCER OF CORPUS AND CERVIX TREATED IN DENMARK 1943—1952

by

KNUD LOCKWOOD and BENT STANCKE

The Danish Cancer Registry was initiated in 1942 and collects notifications from all hospitals in Denmark of cases of malignant neoplasms these include post mortem reports from pathology institutes, and, for cases not admitted to hospital death certificates provided by the National Health Service Since it may be assumed that apart from a few cutaneous neoplasms, no case of cancer will be cured without passing through a hospital general practitioners are not asked to join this completely voluntary organization It may be assumed that all cases of malignant neoplasms have been listed in the registry with the exception of some cases of cancer of the skin (CLEMMESEN 1965)

The tables accompanying this paper indicate that uterine cancer in Denmark is to a large extent being treated in one of three radium centres which are units confined to radiotherapy within larger hospitals Many cases are referred by general practitioners directly to these units Surgical treatment although available within the hospitals where the radium centres are located has not been specialized to a corresponding degree It follows that radio

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Knud Lo...

The Danish Cancer Re... tions from all hospitals ... include post mortem rep... admitted to hospital ... Service Since it may be a... no case of cancer will b... practitioners are not ask... It may be assumed that ... in the registry with the ... MESEN 1965)

The tables accompany... mark is to a large extent ... are units confined to ra... referred by general pract... although available within ... has not been specialized ...

From the Danish Cancer R... Denmark Submitted for p...

Table 1

... reported during the period 1943—1952

...noma of uterine ...x		Carcinoma of uterine body	
...ber of	Per cent	Number of cases	Per cent
	100 0	2 226	100 0
	9? 9	1 920	86 3
	7 1	306	13 7
	0 7	26	1 2
	0 4	19	0 8
	3 6	125	5 6
	2 1	122	5 5
	0 3	14	0 6

...on were negligible Some migration ...t will probably not have influenced ... nor can it be presumed to have ... which is fairly uniform throughout ... was therefore deemed sufficiently

...tation of survival rates were the ...alculated after periods of 3 and ...atment While survival rates for ...oportion surviving the period ...ted as relative or corrected ...d mortality for a standard ...954)

...sed

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From the Danish Cancer Registry under the National Anti Cancer league Copenhagen Denmark Submitted for publication 15 October 1965

theraphy will probably have been the first choice during the periods 1943—1947 and 1948—1952

The presentation of survival rates will cover all cases notified to the registry as having been admitted to hospital during the period 1943—1952 for uterine carcinoma, making a total of 8 893 cases, 2 226 of which were located to the body and 6 296 to the cervix of the uterus, 371 were unspecified The information available from the files of the registry had often to be supplemented with direct inquiries to hospitals and population registries to find out if the patients were alive in January 1962

Full information was available for 1 190, or 86 3 % of 2 226 cases diagnosed as carcinoma of the body of the uterus, while 6 296 cases classed as cervical carcinoma were reduced to 5 848 confirmed cases, or 92 9 % The exclusion, due to inadequate information of 13 7 % and 7 1 %, respectively, affected mainly the older age groups and patients in advanced stages of the disease

Information on the clinical stage was collected on all cases for which it had not been reported to the registry and the opportunity was taken to exclude cases of carcinoma in situ and other pre invasive stages For corpus carcinoma the grouping according to stage was stage I, localized tumour, stage II, tumour with regional spread, stage III, tumour with distant metastases For cervical carcinoma the staging followed the criteria originally laid down, as follows, by the League of Nations

Stages

I — carcinoma strictly confined to cervix

II — carcinoma extends beyond cervix but has not reached pelvic wall, or involves vagina but not the lower third

III — carcinoma has reached pelvic wall (on rectal examination no 'cancer-free space between tumour and pelvic wall), or carcinoma involves the lower third of vagina

IV — carcinoma involves bladder or rectum, or both, or has extended beyond limits previously described

Ideally, all cases ought to be grouped according to stage when first seen and staging should be carried out by clinical means This procedure seems in practice to be followed only by radiotherapists while surgeons are generally influenced by findings at operation or by pathologic specimens

The study covered the two periods of 1943—1947 and 1948—1952 and the observation time was 9 years Some extension in the use of histologic investigation and other methods for verification of diagnosis occurred during the study but will presumably not have caused any systematic change in the material This covered all parts of metropolitan Denmark during a limited

Table 1

Validity of information in all cases reported during the period 1943—1952

	Carcinoma of uterine cervix		Carcinoma of uterine body	
	Number of cases	Per cent	Number of cases	Per cent
Total specified by site	6 296	100 0	2 226	100 0
Complete data total	5 848	92 9	1 920	86 3
Incomplete data total	448	7 1	306	13 7
Death certificate only	46	0 7	26	1 2
Post mortem report only	25	0 4	19	0 8
Treatment not stated	227	3 6	125	5 6
Stage not stated	131	2 1	122	5 5
Otherwise deficient	19	0 3	14	0 6

period when emigration and immigration were negligible Some migration from rural to urban areas did occur but will probably not have influenced the social features determining incidence, nor can it be presumed to have caused any difference in access to therapy which is fairly uniform throughout the country The material on the whole was therefore deemed sufficiently uniform for our purpose

Technique The methods used for computation of survival rates were the standard actuarial procedures Rates were calculated after periods of 3 and 6 months and annually up to 9 years after treatment While survival rates for the first 3 and 6 months were calculated as proportion surviving the period, those for the remaining periods were calculated as relative or corrected survival rates based upon the age distributed mortality for a standard population (Denmark 1945—1949 and 1950—1954)

The following designations and formulas were used

L_x number of cases at beginning of period X

D_x number of deaths during period X

$q = \frac{D_x}{L_x}$ crude death rate for period X

$p_x = 1 - q_x$ crude survival rate for period X

p_x^* probability of survival during period X for a standard population with the same age distribution

$R_x = \frac{p_x}{p_x^*}$ corrected survival rate

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Stages

I — carcinoma strictly confined to cervix

II — carcinoma extends beyond cervix but has not reached pelvic wall, or involves vagina but not the lower third

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Table 1

Validity of information in all cases reported during the period 19[illegible]

	Carcinoma of uterine cervix		Carcinoma of corpus [illegible]	
	Number of cases	Per cent	Number of cases	Per cent
Total reported by site	6 296	100 0	[illegible]	[illegible]
Complete data total	5 848	92.9	[illegible]	[illegible]
Incomplete data total	448	7 1	[illegible]	[illegible]
Death certificate only	46	0 7	[illegible]	[illegible]
Post-mortem report only	25	0 4	[illegible]	[illegible]
Treatment not stated	[illegible]	3 6	[illegible]	[illegible]
Stage not stated	131	2 1	[illegible]	[illegible]
Otherwise deficient	19	0 3	[illegible]	[illegible]

period when emigration and immigration were negligible. Some [illegible] from rural to urban areas did occur but will probably not [illegible] the social features determining incidence nor can it be presumed [illegible] caused any difference in access to therapy, which is fairly [illegible] the country The material on the whole was therefore deemed [illegible] uniform for our purpose

Technique The methods used for computation of survival [illegible] standard actuarial procedures Rates were calculated after [illegible] 6 months and annually up to 9 years after treatment While [illegible] the first 3 and 6 months were calculated as proportion surviving [illegible] those for the remaining periods were calculated as relative [illegible] survival rates, based upon the age distributed mortality [illegible] population (Denmark 1945—1949 and 1950—1954)

The following designations and formulas were used

L_x number of cases at beginning of period x

D_x number of deaths during period x

$q = \frac{D_x}{L_x}$ crude death rate for period x

$p_x = 1 - q_x$ crude survival rate for period x

p_x^* probability of survival during period x [illegible] tion with the same age distribution

$R_x = \frac{p_x}{p_x^*}$ corrected survival rate

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The presentation of survival rates will cover all cases notified to the registry as having been admitted to hospital during the period 1943—1952 for uterine carcinoma, *making a total of 8 893 cases, 2 226 of which were located to the* body and 6 296 to the cervix of the uterus, 371 were unspecified The information available from the files of the registry had often to be supplemented with direct inquiries to hospitals and population registries to find out if the patients were alive in January 1962

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Stages

I — carcinoma strictly confined to cervix

II — carcinoma extends beyond cervix but has not reached pelvic wall, or involves vagina but not the lower third

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Ideally, all cases ought to be grouped according to stage when first seen and staging should be carried out by clinical means This procedure seems in practice to be followed only by radiotherapists while surgeons are generally influenced by findings at operation or by pathologic specimens

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Table 1

Validity of information [illegible] cases reported [illegible] according to stage -1952

	Carcinoma [illegible] cervix		[illegible]		Stage IV	
	Number of cases	[illegible]	[illegible] cases	[illegible]	Numbers	%
Total specified by site	6[illegible]	[illegible]	[illegible]			
Complete data total	5848	[illegible]	[illegible]		96	61 1
Incomplete data, total	418	1	[illegible]	[illegible]	10	48 7
Death certificate only	[illegible]	[illegible]	[illegible]	1		
Post mortem report only	25	[illegible]	[illegible]	1		
Treatment not stated	223	[illegible]	[illegible]	[illegible]	3	23 8
Stage not stated	131	21	[illegible]		7	32 2
Otherwise deficient	19	[illegible]	[illegible]			
						15 1
						19 1

period when emigration and immigration were [illegible] from rural to urban areas did occur [illegible] the social features determining incidence, [illegible] caused any difference in access to therapy [illegible] the country The material on the whole was [illegible] uniform for our purpose

Technique The methods used for computation of [illegible] standard actuarial procedures Rates were calculated [illegible] 6 months and annually up to 9 years after treatment [illegible] the first 3 and 6 months were calculated as proportion [illegible] those for the remaining periods were calculated as [illegible] survival rates based upon the age-distribution [illegible] population (Denmark 1945—1949 and 19[illegible]) [illegible] for a standard [illegible] type of

The following designations and formulas were used

L number of cases at beginning of period x

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$p = 1-q$ crude survival rate for period x

p^* probability of survival during period x for a standard population with the same age distribution

$R_x = \frac{p}{p_x^*}$ corrected survival rate

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Table 3a

rs and percentages) of carcinoma of the uterine body listed according to stage atment for each of the periods 1943—1947 and 1948—1952

Stage I		Stage II		Stage III		Stage IV	
Num bers		Num bers		Num bers		Num- bers	%
366	58 9	84	65 6	46	73 0	496	61 1
384	46 8	125	59 2	31	40 8	540	48 7
173	27 9	11	8 6	9	14 3	193	23 8
0?	36 8	38	18 0	17	2? 3	357	32 2
3?	13 2	33	25 8	8	1? 7	123	15 1
35	16 4	48	22 8	28	36 9	?11	19 1

Table 3b

of carcinoma of the uterine body listed according to stage and type of l outside or within radium centres (the latter in italics)

se I	Stage II		Stage III		Total			
					Cases		Per cent	
28?	13	*71*	14	*32*	111	*385*	13 6	*47 4*
291	20	*105*	7	*24*	1?0	*4?0*	10 8	*37 9*
	11		9		193		23 8	
	38		17		3?7		32 2	
27	19	*14*	3	*5*	77	*46*	9 5	*5 7*
36	33	*15*	18	*10*	150	*61*	13 6	*5 5*

Table 2

Cases of carcinoma of the uterine body listed according to stage in the various age groups during the two study periods

	Number of cases							Total per cent
	Stage I		Stage II		Stage III		Total	
0—39 years								
1943—1947	24		2		2		28	3.4
1948—1952	14		4		2		20	1.8
40—44 years								
1943—1947	40		6		2		48	5.9
1948—1952	37		1		4		42	3.8
45—54 years								
1943—1947	206		29		16		251	30.9
1948—1952	249		50		25		324	29.3
55—64 years								
1943—1947	229		54		22		305	37.6
1948—1952	340		94		24		458	41.3
65—99 years								
1943—1947	122		37		21		180	22.2
1948—1952	181		62		21		264	23.8
Totals								
1943—1947	621	76.5 %	128	15.8 %	63	7.7 %	812	100
1948—1952	821	72.1 %	211	19.0 %	76	6.9 %	1 108	100

$C_x = p_1 \cdot p_2 \ldots$ p_x accumulated survival rates for cases during period $O—X$

$C_x^* = p_1^* \cdot p_2^* \ldots$ p_x^* accumulated probability of survival for a standard population with the same age distribution as patients during period $O—X$

$CR_x = \frac{C_x}{C_x^*}$ corrected survival rate for patients during period $O—X$

p_x $(X = 3$ months$)$ 3 month survival rates

CR_x $(X = 1, 3, 5,$ and 9 years$)$ one, three five and nine year survival rates

It should be noted that the electronic technique employed made it possible to adjust for general mortality so that survival rates apply exclusively to the uterine carcinoma in question when entered as the main cause of death

Table 3a

Distribution of cases (numbers and percentages) of carcinoma of the uterine body listed according to stage and type of treatment for each of the periods 1943—1947 and 1948—1952

	Stage I		Stage II		Stage III		Stage IV	
	Numbers	%	Numbers		Numbers		Numbers	%
Radiotherapy								
1943—1947	366	58 9	84	65 6	46	73 0	496	61 1
1948—1952	384	46 8	125	59 2	31	40 8	540	48 7
Surgery								
1943—1947	173	27 9	11	8 6	9	14 3	193	23 8
1948—1952	302	36 8	38	18 0	17	22 3	357	32 2
Surgery and irradiation								
1943—1947	82	13 2	33	25 8	8	12 7	123	15 1
1948—1952	135	16 4	48	22 8	28	36 9	211	19 1

Table 3b

Distribution of cases (numbers) of carcinoma of the uterine body listed according to stage and type of treatment as applied outside or within radium centres (the latter in italics)

	Stage I		Stage II		Stage III		Total			
							Cases		Per cent	
Radiotherapy										
1943—1947	84	*282*	13	*71*	14	*37*	111	*385*	13 6	*47 4*
1948—1952	93	*291*	20	*105*	7	*24*	120	*4 0*	10 8	*37 9*
Surgery										
1943—1947	173		11		9		193		23 8	
1948—1952	302		38		17		357		32 2	
Surgery and irradiation										
1943—1947	55	*27*	19	*14*	3	*5*	77	*46*	9 5	*5 7*
1948—1952	99	*36*	33	*15*	18	*10*	150	*61*	13 6	*5 5*

Table 4

Survival rates in carcinoma of the uterine body, stage I for different age groups as related to treatment with radiotherapy alone outside of radium centres and with radiotherapy and surgery, respectively within radium centres (the latter in italics)

	Survival rates					
	Total		9 years		3 months	
0—44 years						
Radiotherapy						
1943—1947	2	*17*	2	13	1.00	0.94
1948—1952	5	*6*	3	4	1.00	*1.00*
Surgery						
1943—1947		*31*		*27*		*0.94*
1948—1952		*28*		*26*		*1.00*
45—54 years						
Radiotherapy						
1943—1947	16	*79*	11	*48*	1.00	*0.99*
1948—1952	21	*69*	15	*49*	1.00	*1.00*
Surgery						
1943—1947		*73*		*58*		*0.95*
1948—1952		*121*		*112*		*0.97*
55—64 years						
Radiotherapy						
1943—1947	42	*115*	27	*52*	0.95	*0.98*
1948—1952	34	*117*	21	*50*	0.97	*0.98*
Surgery						
1943—1947		*51*		*29*		*0.94*
1948—1952		*119*		*81*		*0.93*
65—99 years						
Radiotherapy						
1943—1947	33	*71*	9	*10*	0.97	*0.97*
1948—1952	24	*99*	7	*14*	0.92	*0.93*
Surgery						
1943—1947		*18*		*7*		*0.78*
1948—1952		*34*		*15*		*0.94*

Table 4 *(cont)*

1 years		3 years		5 years		9 years	
1 00	0 89	1 00	0 83	1 00	0 78	1 00	0 79
1 00	0 84	0 81	0 84	0 81	0 68	0 62	0 69
	0 94		*0 91*		*0 9[illegible]*		*0 90*
	1 00		*0 97*		*0 94*		*0 95*
1 01	*0 97*	0 83	*0 87*	0 84	*0 77*	0 73	*0 66*
0 91	*1 01*	0 83	*0 85*	0 79	*0 8[illegible]*	0 78	*0 76*
	0 94		*0 88*		*0 86*		*0 85*
	0 9[illegible]		*0 97*		*0 96*		*0 99*
0 89	*0 88*	0 8[illegible]	*0 70*	0 85	*0 59*	0 77	*0 55*
0 89	*0 87*	0 74	*0 68*	0 73	*0 56*	0 73	*0 50*
	0 87		*0 76*		*0 7[illegible]*		*0 [illegible]8*
	0 91		*0 85*		*0 85*		*0 79*
0 9[illegible]	*0 92*	0 90	*0 68*	0 70	*0 57*	0 47	*0 27*
0 78	*0 82*	0 58	*0 63*	0 43	*0 4[illegible]*	0 51	*0 27*
	0 80		*0 75*		*0 69*		*0 62*
	0 8		*0 73*		*0 67*		*0 73*

Table 5

Survival rates in carcinoma of the uterine body, stages II and III for different age groups treated with radiotherapy and surgery in radium centres during 1943—1952

	Cases				Survival rates	
	Total		9 year survivors		3 months	
	II	III	II	III	II	III
0—44 years						
Radiotherapy	6	3	1	—	1.00	0.67
Surgery	2	—	1	—	1.00	—
45—54 years						
Radiotherapy	28	14	11	1	0.96	0.57
Surgery	20	7	15	1	0.95	0.86
55—64 years						
Radiotherapy	78	15	20	1	0.94	0.73
Surgery	17	9	9	1	0.88	0.44
65—99 years						
Radiotherapy	64	24	4	—	0.81	0.71
Surgery	10	10	2	—	0.90	0.70

Carcinoma of body of uterus

From the first to the second study period of 5 years, the number of cases increased by 30 %, and in the Capital this increase amounted to 48 % in spite of completely unchanged conditions of diagnosis, treatment, and registration.

The data presented and analyzed in the tables have been restricted to cases for which all relevant information was available, and subdivisions have been carried out following the same criteria, i.e. stage, form of treatment, and age group for each of the periods 1943—1947 and 1948—1952.

The distribution of cases according to stages and age groups for each of the two study periods are given in Table 2. It may be noted that the number of fully recorded cases rose from 812 to 1 108, or by 36.5 %. It will further be seen that although the number of cases in all stages progressed, the percentual values increased only in stage II. To suggest that these differences may have affected the comparison does not seem justified, however. On the whole the analysis by age indicates the same trend for all age groups, although some stagnation for the younger age groups below 44 years and a considerable increase in the older age groups is discernible.

Table 5 *(cont.)*

1 year		3 years		5 years		9 years	
II	III	II	III	II	III	II	III
0 84	0 33	0 34	—	0 17	—	0 17	—
1 00	—	1 01	—	0 51	—	0 51	—
0 83	0 29	0 51	0 07	0 41	0 07	0 42	0 08
0 85	0 14	0 82	0 15	0 77	0 15	0 80	0 15
0 74	0 27	0 45	0 14	0 37	0 14	0 30	0 08
0 83	0 11	0 61	0 12	0 57	0 12	0 62	0 13
0 56	0 43	0 35	0 19	0 27	0 11	0 12	—
0 72	0 3[illegible]	0 54	0 12	0 35	—	0 29	—

In Table 3a the distribution of the material according to stages and forms of *treatment* are recorded by numerical values as well as percentages. The treatment has again been subdivided according to three main types: irradiation covering almost half the number of cases of the second study period, pure surgery taking care of nearly one third of the cases *and finally*, the heterogeneous group of combined treatment covering about one fifth of the cases.

A significant change in distribution appears to have taken place during the ten years in *question between stages* within each category of treatment as well as between the various forms of therapy. Thus it is seen that the *combined treatment* increased from 15 1 % to 19 1 % and this applies even more to surgery with an increase from 23 8 % to 32 2 %. *Irradiation,* on the other hand decreased from 61 1 % to 48 7 % although the number of patients undergoing this treatment increased by *slightly less than 10 %* in spite of the general trend towards surgery.

Finally it appears from Table 3a *that a shift* has occurred in the distribution of the stages as represented within each category of treatment. The uneven distribution by stage characteristic for corpus as against cervical

Table 5

Survival rates in carcinoma of the uterine body stages II and III for different age groups treated with radiotherapy and surgery in radium centres during 1943—1952

	Cases				Survival rates	
	Total		9 year survivors		3 months	
	II	III	II	III	II	III
0—44 years						
Radiotherapy	6	3	1	—	1.00	0.67
Surgery	2	—	1	—	1.00	—
45—54 years						
Radiotherapy	28	14	11	1	0.96	0.57
Surgery	20	7	15	1	0.95	0.86
55—64 years						
Radiotherapy	78	15	20	1	0.94	0.73
Surgery	17	9	9	1	0.88	0.44
65—99 years						
Radiotherapy	64	24	4	—	0.81	0.71
Surgery	10	10	2	—	0.90	0.70

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The data presented and analyzed in the tables have been restricted to cases for which all relevant information was available, and subdivisions have been carried out following the same criteria, i.e. stage, form of treatment, and age group for each of the periods 1943—1947 and 1948—1952.

The distribution of cases according to stages and age groups for each of the two study periods are given in Table 2. It may be noted that the number of fully recorded cases rose from 812 to 1 108, or by 36.5 %. It will further be seen that although the number of cases in all stages progressed, the percentual values increased only in stage II. To suggest that these differences may have affected the comparison does not seem justified, however. On the whole, the analysis by age indicates the same trend for all age groups, although some stagnation for the younger age groups below 44 years and a considerable increase in the older age groups is discernible.

Table 5 *(cont)*

1 year		3 years		5 years		9 years	
II	III	II	III	II	III	II	III
0 84	0 33	0 34	—	0 17	—	0 17	—
1 00	—	1 01	—	0 51	—	0 51	—
0 83	0 29	0 51	0 07	0 41	0 07	0 42	0 08
0 85	0 14	0 82	0 15	0 77	0 15	0 80	0 15
0 74	0 27	0 45	0 14	0 37	0 14	0 30	0 08
0 83	0 11	0 61	0 12	0 57	0 12	0 67	0 13
0 56	0 43	0 35	0 19	0 27	0 11	0 12	—
0 7	*0 32*	0 54	0 12	0 35	—	0 29	—

In Table 3a the distribution of the material according to stages and forms of treatment are recorded by numerical values as well as percentages The treatment has again been subdivided according to three main types irradiation covering almost half the number of cases of the second study period pure surgery, taking care of nearly one third of the cases and finally the heterogeneous group of combined treatment covering about one fifth of the cases

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Finally it appears from Table 3a that a shift has occurred in the distribution of the stages as represented within each category of treatment The uneven distribution by stage characteristic for corpus as against cervical

Table 7

Distribution of cases of carcinoma of the uterine cervix listed according to stage in the various age groups during the two study periods

	Number of cases									Total per cent
	Stage I		Stage II		Stage III		Stage IV		Total	
0—39 years										
1943—1947	244		26[illegible]		157		30		694	25 5
1948—1952	341		245		136		64		786	25 1
40—44 years										
1943—1947	144		158		109		36		447	16 4
1948—1952	184		165		111		40		500	16 0
45—54 years										
1943—1947	225		263		234		84		806	29 6
1948—1952	293		286		234		119		932	29 8
55—64 years										
1943—1947	86		174		158		60		478	17 6
1948—1952	132		178		151		76		537	17 2
65—99 years										
1943—1947	58		79		106		52		295	10 9
1948—1952	68		106		126		75		373	11 9
Totals										
1943—1947	757	27.8	937	34 [illegible] %	764	28 1	262	9 6	2 720	100
1948—1952	1 018	32 6 %	980	31 3	758	24 2 %	372	11 9 %	3 128	100

postoperative nature particularly noticeable for older patients those subjected to surgery stand a better chance of survival than those treated by radiotherapy alone This difference increases during the years following treatment Furthermore the survival in irradiated cases has remained approximately the same from the first to the second period of study, while those undergoing operation have undergone a distinct improvement

Results from operation in all age group for the first study period are significantly better than those from radiation for any of the two periods The 121 patients aged between 45 and 54 during the second period have had a survival rate of about 99 % nine years after treatment while the corresponding group of irradiated patients also in stage I, had a survival rate of but 76 % both values having been adjusted for the normally occurring mortality

Table 6

Survival rates in carcinoma of the uterine body stage I for the different age groups given combined treatment during the two study periods

	Number of cases		Survival rates				
	Total	9 year survivors	3 months	1 year	3 years	5 years	9 years
0—44 years							
1943—1947	11	8	1·00	0·91	0·73	0·74	0·75
1948—1952	15	14	1·00	1·00	0·94	0·95	0·96
45—54 years							
1943—1947	33	16	1·00	0·98	0·83	0·72	0·52
1948—1952	43	28	1·00	0·98	0·80	0·74	0·70
55—64 years							
1943—1947	29	9	0·97	0·94	0·65	0·48	0·37
1948—1952	62	25	1·00	0·93	0·72	0·57	0·47
65—99 years							
1943—1947	9	2	1·00	0·81	0·51	0·44	0·40
1948—1952	15	5	0·93	0·89	0·66	0·48	0·52

carcinoma is observed in all three categories of treatment, but it is noticeable that while the first study period contained a considerable excess of cases treated with 'irradiation only' in comparison with 'surgery' the second study period embraced an increase in 'surgery' for stage I while the other stages also displayed some trend in the same direction.

Table 3b illustrates the distribution of cases in each of the three stages for various methods of treatment, those treated in radium centres and those treated elsewhere being separated. This provides a detailed survey of groups entering survival rate tables, i.e. for pure radiotherapy in or outside radium centres, for surgery outside radium centres, and for cases subjected to combined treatment, whether totally or partly outside radium centres. An increase in the absolute number of cases occurred in all these groups during the period of study.

Table 4 gives the number of cases treated in stage I distributed in four age groups by category of treatment, the survival rates being computed for each study period.

It is evident that the chance of survival with radiotherapy and surgery fundamentally differs. In spite of the somewhat larger initial mortality of

Table 7

Distribution of cases of carcinoma of the uterine cervix listed according to stage in the various age groups during the two study periods

	Number of cases					Total per cent
	Stage I	Stage II	Stage III	Stage IV	Total	
0—39 years						
1943—1947	244	263	157	30	694	25 5
1948—1952	341	245	136	64	786	25 1
40—44 years						
1943—1947	144	158	109	36	447	16 4
1948—1952	184	165	111	40	500	16 0
45—54 years						
1943—1947	275	263	234	84	806	29 6
1948—1952	293	286	234	119	932	29 8
55—64 years						
194 —1947	86	174	158	60	478	17 6
1948—1952	132	178	151	76	537	17 2
65—99 years						
1943—1947	58	79	106	52	295	10 9
1948—1952	68	106	126	75	373	11 9
Totals						
1943 1947	757 27 8	937 34 5 %	764 28 1	262 9 6	2 720	100
1948—1952	1 018 32 6 %	980 31 3 %	758 24 2 %	372 11 9	3 128	100

postoperative nature particularly noticeable for older patients, those subjected to surgery stand a better chance of survival than those treated by radiotherapy alone This difference increases during the years following treatment Furthermore the survival in irradiated cases has remained approximately the same from the first to the second period of study while those undergoing operation have undergone a distinct improvement

Results from operation in all age groups for the first study period are significantly better than those from radiation for any of the two periods The 121 patients aged between 45 and 54 during the second period have had a survival rate of about 99 % nine years after treatment while the corresponding group of irradiated patients also in stage I had a survival rate of but 76 %, both values having been adjusted for the normally occurring mortality

Table 8a

Distribution of cases (numbers and percentages) of carcinoma of the uterine cervix listed according to stage and type of treatment for each of the two study periods

	Stage I		Stage II		Stage III		Stage IV		Total	
	Nos	%	Nos	%	Nos	%	Nos	%	Nos	%
Radiotherapy										
1943—1947	690	91.1	875	93.4	725	94.9	255	97.3	2 545	93.6
1948—1952	824	81.0	903	92.2	706	93.1	348	93.6	2 781	88.9
Surgery										
1943—1947	21	2.8	11	1.2	8	1.0	1	0.4	41	1.5
1948—1952	99	9.7	22	2.2	9	1.2	3	0.8	133	4.3
Surgery and irradiation										
1943—1947	46	6.1	51	5.4	31	4.1	6	2.3	134	4.9
1948—1952	95	9.3	55	5.6	43	5.7	21	5.6	214	6.8

The corresponding values for radiotherapy outside radium centres are given in italics in Table 4.

Table 5 gives the survival rates for stages II and III for age groups corresponding to those in Table 4. The over-all tendency is the same as for stage I although the differences in survival rates between the two forms of treatment are even more marked. The absolute number of survivors treated in stage I with combined treatment are given separately in Table 6.

Carcinoma of the cervix

Table 7 gives the distribution by age and stage for the 5 848 cases of cervical carcinoma for which all data were available for each of the study periods 1943—1947 and 1948—1952. While the Danish population as a whole increased by about 6 % during the years in question, the increase in cases of cervical carcinoma amounted to 15 %. Although no pre-invasive cases entered the study, more than half of this increase referred to cases grouped under stage I, presumably due to the more efficient diagnosis in early cases. The figures for stages II and III remained more or less stationary during the study period, while cases grouped under stage IV increased with about a third.

Table 8a presents the distribution of cervical cancer cases by stage and

Table 8b

Distribution of cases (numbers) of carcinoma of the uterine cervix listed according to stage and type of treatment as applied outside or within radium centres (the latter in italics)

	Number of cases										Total per cent	
	Stage I		Stage II		Stage III		Stage IV		Total			
Radiotherapy												
1943—1947	84	*606*	68	*807*	84	*641*	19	*236*	255	*2 290*	9 4	*84 2*
1948—1952	108	*716*	80	*823*	64	*642*	22	*3[illegible]6*	274	*2 507*	8 8	*80 1*
Surgery												
1943—1947	21		11		8		1		41		1 [illegible]	
1948—1952	99		22		9		3		133		4 3	
Surgery and irradiation												
1943—1947	13	*33*	7	*44*	9	*22*	—	*6*	29	*105*	*1 1*	*3 8*
1948—1952	34	*61*	16	*39*	6	*37*	8	*13*	64	*150*	2 0	*4 8*
Total												
1943—1947	757		937		*764*		*26[illegible]*		*2 720*		*100*	
1948—1952	1 018		980		758		372		3 128		100	

form of treatment irrespective of hospital category as well as the corresponding percentage values for each of the two periods studied An outstanding feature is the threefold increase in the numbers subjected to surgical treatment although reaching *only* 4 3 % of all cases treated This increase is, however unevenly distributed by stage since it affects mainly the two earliest stages in particular the first The number of patients treated by radiotherapy also increased although roughly proportionately to the totals for stages I II, and IV The same applies largely to the group receiving combined treatment, which incidentally increased by about 50 %

Table 8b gives the number of cases of cervical carcinoma for each stage and five year period according to the type of treatment given in radium centres or elsewhere respectively The *table* reveals that more than 75 % of cases received radiotherapy in radium centres while 4 3 % or 133 cases, were treated by radical surgery alone during the second period of study The remainder, about 10 % were treated with radiotherapy alone outside radium centres or had combined treatment wholly or partly outside of these units These data form the basis of the presentation of survival rates given in Tables 9 to 11

The stage I cases treated at radium centres with radiotherapy for cervical

Table 8a

Distribution of cases (numbers and percentages) of carcinoma of the uterine cervix listed according to stage and type of treatment for each of the two study periods

	Stage I		Stage II		Stage III		Stage IV		Total	
	Nos	%	Nos	%	Nos	%	Nos	%	Nos	%
Radiotherapy										
1943—1947	690	91 1	875	93 4	725	94 9	255	97 3	2 545	93 6
1948—1952	824	81 0	903	92 2	706	93 1	348	93 6	2 781	88 9
Surgery										
1943—1947	21	2 8	11	1 2	8	1 0	1	0 4	41	1 5
1948—1952	99	9 7	22	2 2	9	1 2	3	0 8	133	4 3
Surgery and irradiation										
1943—1947	46	6 1	51	5 4	31	4 1	6	2 3	134	4 9
1948—1952	95	9 3	55	5 6	43	5 7	21	5 6	214	6 8

The corresponding values for radiotherapy outside radium centres are given in italics in Table 4

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Carcinoma of the cervix

Table 7 gives the distribution by age and stage for the 5 848 cases of cervical carcinoma for which all data were available for each of the study periods 1943—1947 and 1948—1952 While the Danish population as a whole increased by about 6 % during the years in question, the increase in cases of cervical carcinoma amounted to 15 % Although no pre invasive cases entered the study, more than half of this increase referred to cases grouped under stage I, presumably due to the more efficient diagnosis in early cases The figures for stages II and III remained more or less stationary during the study period, while cases grouped under stage IV increased with about a third

Table 8a presents the distribution of cervical cancer cases by stage and

Table 8b

Distribution of cases (numbers) of carcinoma of the uterine cervix listed according to stage and type of treatment as applied outside or within radium centres (the latter in italics)

	Number of cases										Total per cent	
	Stage I		Stage II		Stage III		Stage IV		Total			
Radiotherapy												
1943—1947	84	*606*	68	*807*	84	*641*	19	*236*	255	*2 290*	9 4	*84 2*
1948—1952	108	*716*	80	*823*	64	*642*	22	*326*	274	*2 507*	8 8	*80 1*
Surgery												
1943—1947	21		11		8		1		41		1 5	
1948—1952	99		22		9		3		133		4 3	
Surgery and irradiation												
1943—1947	13	*33*	7	*44*	9	*22*	—	*6*	29	*105*	1 1	*3 8*
1948—1952	34	*61*	16	*39*	6	*37*	8	*13*	64	*150*	2 0	*4 8*
Total												
1943—1947	757		937		764		262		2 720		100	
1948—1952	1 018		980		758		372		3 128		100	

form of treatment, irrespective of hospital category, as well as the corresponding percentage values for each of the two periods studied An outstanding feature is the threefold increase in the numbers subjected to surgical treatment, although reaching only 4 3 % of all cases treated This increase is, however unevenly distributed by stage since it affects mainly the two earliest stages, in particular the first The number of patients treated by radiotherapy also increased although roughly proportionately to the totals for stages I II, and IV The same applies largely to the group receiving combined treatment which incidentally increased by about 50 %

Table 8b gives the number of cases of cervical carcinoma for each stage and five year period according to the type of treatment given in radium centres or elsewhere respectively The table reveals that more than 75 % of cases received radiotherapy in radium centres while 4 3 % or 133 cases, were treated by radical surgery alone during the second period of study The remainder, about 10 % were treated with radiotherapy alone outside radium centres or had combined treatment wholly or partly outside of these units These data form the basis of the presentation of survival rates given in Tables 9 to 11

The stage I cases treated at radium centres with radiotherapy for cervical

Table 10

Survival rates in carcinoma of the uterine cervix stages III and IV, for different age groups treated in radium centres during the two study periods

	Number of cases				Rates of survivals in	
	Total		9 year survivors		3 months	
	III	IV	III	IV	III	IV
0—39 years						
1943—1947	131	27	41	7	0.96	0.81
1948—1952	107	55	38	4	0.95	0.82
40—44 years						
1943—1947	91	31	29	10	0.92	0.81
1948—1952	92	33	37	9	0.98	0.88
45—54 years						
1943—1947	199	76	58	17	0.90	0.79
1948—1952	203	107	83	24	0.98	0.88
55—64 years						
1943—1947	125	56	36	5	0.92	0.80
1948—1952	132	68	45	10	0.95	0.79
65—99 years						
1943—1947	95	46	16	1	0.82	0.67
1948—1952	108	63	15	5	0.94	0.76

peutic treatment However, the small number of cases and the absence of uniformity make the data unsuited for computations One reason for this heterogeneity is that the two forms of treatment were in a number of cases instituted at considerable and varying intervals of time, which makes it doubtful whether any curative therapy was really intended or performed Some cases may primarily have been considered suitable for operation but later inoperable and referred for radiotherapy

Table 12 summarizes results for stage I during the last period of study, for operated and for irradiated cases in the age groups 0—44 and 45—64 years For the sake of uniformity, only cases irradiated at radium centres have been included and the category of operated cases has been restricted to those subjected to operation designated as 'radical' but without any further specification There is reason to believe that not all patients were subjected to the so called extended Wertheim's operation, which in Denmark is performed only in a few highly specialized hospital departments In consequence the

Table 10 *(cont)*

per cent							
1 year		3 years		5 years		9 years	
III	IV	III	IV	III	IV	III	IV
0 60	0 45	0 41	0 [illegible]6	0 36	0 26	0 32	0 27
0 62	0 38	0 40	0 15	0 38	0 09	0 36	0 07
0 68	0 58	0 43	0 42	0 37	0 33	0 33	0 34
0 74	0 55	0 48	0 40	0 46	0 34	0 42	0 28
0 66	0 57	0 39	0 34	0 34	0 30	0 31	0 24
0 76	0 53	0 53	0 31	0 48	0 25	0 43	0 24
0 75	0 42	0 48	0 19	0 37	0 14	0 34	0 11
0 77	0 54	0 52	0 32	0 44	0 22	0 40	0 17
0 59	0 39	0 36	0 08	0 34	0 06	0 32	—
0 67	0 42	0 44	0 28	0 38	0 15	0 25	0 15

surgical data do not represent a material as uniform as the radiotherapeutic nevertheless the data for stage I may be considered sufficiently representative for analysis

It is evident from the Tables 9 and 12 that survival rates for the two groups of cases differ significantly It is true that the 3 month survival rate influenced as it is by operation mortality is slightly higher for irradiated patients particularly in the older groups but already after one year the rates for the operated cases exceed those for irradiated cases and this difference is accentuated during the entire period of study

Discussion

It is essential before considering the results to decide whether the data for the two major methods of treatment radiotherapy and surgery are comparable or whether some selection may have influenced results significantly It

Table 10

Survival rates in carcinoma of the uterine cervix stages III and IV, for different age groups treated in radium centres during the two study periods

	Number of cases				Rates of survivals in	
	Total		9 year survivors		3 months	
	III	IV	III	IV	III	IV
0—39 years						
1943—1947	131	27	41	7	0.96	0.81
1948—1952	107	55	38	4	0.95	0.82
40—44 years						
1943—1947	91	31	29	10	0.92	0.81
1948—1952	92	33	37	9	0.98	0.88
45—54 years						
1943—1947	199	76	58	17	0.90	0.79
1948—1952	203	107	83	24	0.98	0.88
55—64 years						
1943—1947	125	56	36	5	0.92	0.80
1948—1952	132	68	45	10	0.95	0.79
65—99 years						
1943—1947	95	46	16	1	0.82	0.67
1948—1952	108	63	15	5	0.91	0.76

peutic treatment However, the small number of cases and the absence of uniformity make the data unsuited for computations One reason for this heterogeneity is that the two forms of treatment were in a number of cases instituted at considerable and varying intervals of time, which makes it doubtful whether any curative therapy was really intended or performed Some cases may primarily have been considered suitable for operation but later inoperable and referred for radiotherapy

Table 12 summarizes results for stage I during the last period of study, for operated and for irradiated cases in the age groups 0—44 and 45—64 years For the sake of uniformity, only cases irradiated at radium centres have been included and the category of operated cases has been restricted to those subjected to operation designated as 'radical but without any further specification There is reason to believe that not all patients were subjected to the so called extended Wertheim s operation, which in Denmark is performed only in a few highly specialized hospital departments In consequence, the

Table 10 [illegible]

per cent							
1 ye r		3 [illegible]		[illegible]		[illegible]	
III	IV	III	I[illegible]	III			
0 60	0 45	0 41	[illegible]	[illegible]	—		
0 67	0 38	0 40	[illegible]	[illegible]			
0 68	0 58	0 43	[illegible]	[illegible]			
0 74	0 55	0 48	[illegible]	[illegible]	[illegible]		
0 66	0 57	[illegible]	[illegible]	[illegible]	[illegible]		
0 76	0 53	0 53	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0 75	0 42	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0 77	0 54	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0 59	0 39	0 36	[illegible]	[illegible]	[illegible]	[illegible]	
0 67	0 42	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]

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Discussion

It is essential befor[e] considering the results to decide whether the data for the two major methods of treatment radiotherapy and surgery, are compar[a]ble or whether som[e] selectio[n] may have influenced resul[t]s significantl[y]

Table 10

Survival rates in carcinoma of the uterine cervix stages III and IV, for different age groups treated in radium centres during the two study periods

	Number of cases				Rates of survivals in	
	Total		9 year survivors		3 months	
	III	IV	III	IV	III	IV
0—39 years						
1943—1947	131	27	41	7	0 96	0 81
1948—1952	107	55	38	4	0 95	0 82
40—44 years						
1943—1947	91	31	29	10	0 92	0 81
1948—1952	92	33	37	9	0 98	0 88
45—54 years						
1943—1947	199	76	58	17	0 90	0 79
1948—1952	203	107	83	24	0 98	0 88
55—64 years						
1943—1947	125	56	36	5	0 92	0 80
1948—1952	132	68	45	10	0 95	0 79
65—99 years						
1943—1947	95	46	16	1	0 82	0 67
1948—1952	108	63	15	5	0 94	0 76

peutic treatment However, the small number of cases and the absence of uniformity make the data unsuited for computations One reason for this heterogeneity is that the two forms of treatment were in a number of cases instituted at considerable and varying intervals of time, which makes it doubtful whether any curative therapy was really intended or performed Some cases may primarily have been considered suitable for operation but later inoperable and referred for radiotherapy

Table 12 summarizes results for stage I during the last period of study, for operated and for irradiated cases in the age groups 0—44 and 45—64 years For the sake of uniformity, only cases irradiated at radium centres have been included and the category of operated cases has been restricted to those subjected to operation designated as radical but without any further speci fication There is reason to believe that not all patients were subjected to the so called extended Wertheim's operation which in Denmark is performed only in a few highly specialized hospital departments In consequence, the

Table 1

Values in mm Hg obtained in measurements of the ventricular fluid pressure in Case 1 before treatment and during delivery of each dose

No. of treatment	Before treatment	Minutes after the onset of treatment								
		1	2	3	4	5	6	7	8	9
I	30	31	32	34	33	33	34	33	34	
II	30	28	31	31	35	37	35	35	42	48
III	50	42	36	32	28	31	30	27	29	32
IV	22	25	30	24	24	30	30	28	30	
V	24	32	30	29	32	32	39	32	36	36
Mean values	31±5	32±3	32±1	30±2	30±2	33±1	34±2	31±2	34±2	38

Table 2

Total protein content of the ventricular fluid before and during irradiation of the tumour in Case 1

Date	Roentgen treatment	Colour	Cells			Protein		Total protein mg %
			Polyn	Monon	RBC	Nonne	Pandy	
16/11	—	Flakes	0	0	0	Neg	Neg	6
17/11	—	»	0	0	0	Neg	Slight pos	1
18/11	—	»	0	0	0	Neg	Neg	8
19/11	—	»	0	0	Some fresh	Neg	Neg	10
20/11	+	»	0	0.6	0	Neg	Neg	9
21/11	+	»	0	0	0	Neg	Neg	9
22/11		»	0	0	0	Neg	Neg	10
23/11	+	»	0.6	0	0	Neg	Neg	9
24/11	+	»	0	0	0	Neg	Neg	9
25/11	+	»	0	0.6	0	Neg	Neg	10

Table 3

Values in mm Hg obtained in measurements of the ventricular fluid pressure in Case 2 before treatment and during delivery of each dose

Treatment No.	Before treatment	Minutes after the onset of treatment						
		1	2	3	4	5	6	7
I—VI not measured								
VII	45	70	38	24	21	40	46	46
VIII	30	25	26	25	30	18	20	22
IX	55	55	58	60	62	58	65	34
Mean values	43	50	41	36	38	39	44	34

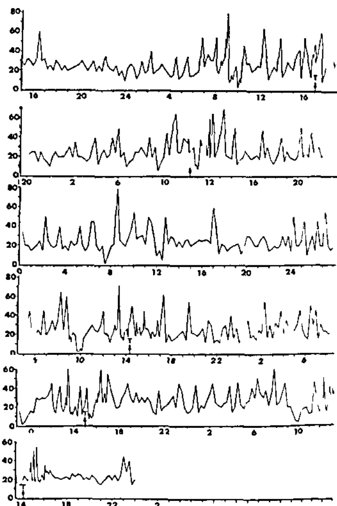


Fig. 1. Case 1. Ventricular fluid pressure recorded continuously before and during the first days of treatment. The time of irradiation is indicated by T. mm Hg on the ordinate and the time of the day on the abscissa.

The standard error of the mean value in Figs. 4 and 5, indicated as vertical bars, was obtained from the formula

$$\varepsilon = \sqrt{\Sigma (x - \bar{x})^2 / n\ (n - 1)}$$

where ε is the standard error of the mean, $\Sigma (x - \bar{x})^2$ is the sum of the squared deviations from the mean, and n the number of observations.

When two mean values, $\bar{x}_1 - \bar{x}$, were compared, the significance of the difference was calculated from the error of the difference

$$\varepsilon_{(\bar{x} - \bar{x}_1)} = \sqrt{\varepsilon^2_{(\bar{x}_1)} + \varepsilon^2_{(\bar{x})}}$$

The difference was accepted to be statistically significant if $\dfrac{|\bar{x}_1 - \bar{x}|}{\varepsilon_{(\bar{x}_1 - \bar{x})}}$ exceeded 2.6.

Table 1

Values in mm Hg obtained in measurements of the ventricular fluid pressure in Case 1 before treatment and during delivery of each dose

No. of treatment	Before treatment	Minutes after the onset of treatment								
		1	2	3	4	5	6	7	8	9
I	30	31	32	34	33	33	34	33	34	
II	30	28	31	31	35	37	35	35	42	48
III	50	42	36	32	28	31	30	27	29	32
IV	22	25	30	24	24	30	30	28	30	
V	24	32	30	29	32	32	39	32	36	36
Mean values	31±5	32±3	32±1	30±2	30±2	33±1	34±2	31±2	34±2	38

Table 2

Total protein content of the ventricular fluid before and during irradiation of the tumour in Case 1

Date	Roentgen treatment	Colour	Cells			Protein		Total protein mg %
			Polyn	Monon	RBC	Nonne	Pandy	
16/11	—	Flakes	0	0	0	Neg	Neg	6
17/11	—	»	0	0	0	Neg	Slight pos	1
18/11	—	»	0	0	0	Neg	Ne	8
19/11	—	»	0	0	Some fresh	Neg	Neg	10
20/11	+	»	0	0.6	0	Neg	Neg	9
21/11	+	»	0	0	0	Neg	Neg	9
22/11		»	0	0	0	Neg	Neg	10
23/11	+	»	0.6	0	0	Neg	Neg	9
24/11	+	»	0	0	0	Neg	Neg	9
25/11	+	»	0	0.6	0	Neg	Neg	10

Table 3

Values in mm Hg obtained in measurements of the ventricular fluid pressure in Case 2 before treatment and during delivery of each dose

Treatment No.	Before treatment	Minutes after the onset of treatment						
		1	2	3	4	5	6	7
I—VI not measured								
VII	45	70	38	24	21	40	46	46
VIII	30	25	26	25	30	18	20	22
IX	55	55	58	60	62	58	65	34
Mean values	43	50	41	36	38	39	44	34

Table 3

Soft tissue tumours in mated and unmated groups

Tumour type		Unmated mice n 97	Mated mice n 97
Squamous-cell carcinoma		2	6
Adenoma of the lung		1	5
Adenoma of the ovary		—	2
Pituitary adenoma		—	2
Tumour of the adrenal medulla		1	—
Ependymoma		—	1
Fibrosarcoma		—	1
Leukemia		1	10
Thymoma		—	1
	Total	5 (5 2 %)	28 (28 9 %)

leucocyte count was made using a Spencer haemocytometer (from American Optical) The haemoglobin content was examined in a Ljungberg colorimeter and the results obtained in per cent were recalculated in gram per 100 *ml* blood

The mice were radiographed in the dorso ventral position, using Structurix or Os ray film for localizing tumours during dissection The carcasses and also the kidneys adrenal bodies spleens and thymuses were weighed

Fixation in Sieve s fluid and decalcification in 20 % formic acid was per formed on the tissues Conventional histologic methods were used the sections being stained according to the van Gieson method with Ehrlich s haematoxylin eosin, and Lillie s azur eosinate

The tumour material includes intramedullary osteosarcoma buds (Fig 1) because earlier investigations (NILSSON 1962 NILSSON 1966) have shown that these buds are growing autonomous entities All intramedullary situated foci of proliferation containing pleomorphic cell elements have thus been considered as osteosarcomas

Marrow was examined from the distal end of the femur and from the 6th lumbar vertebra All the marrow preparations were photographed and studied at × 200 magnification They were compared with an arbitrary scale as follows

Scale	0	+ 1 and 2 and 3	+4	+ 5
	Aplasia	Hypoplasia	Normal	Hyperplasia

injection the animals were divided into two groups, with 100 animals in each, and ear marked. One group was mated, in which case three females and one male were put together in one cage. Each litter was separated from its mother after a suckling period of 21 days. Immediately after weaning, the mothers were again mated according to the same system. The total length of the mating period was spread over 224 days, during which time the hundred mated females gave 4 to 10 litters and a total number of 4 227 young. For details, see Table 2. The other group of 100 mice was used as the unmated control series.

In addition, a group of 100 animals without ^{90}Sr treatment were used as a control of the natural incidence of malignancies.

During the experiment, the animals were fed on a standard diet ad libitum and kept under similar environmental conditions in the same room. The control series was housed in groups of ten animals per cage throughout the entire experiment, and the mated series likewise after the mating period. Three mice were lost from each group. The following numbers of skeleton samples from the remaining mice in each group were selected and examined histologically.

	Mated mice	Unmated mice
Femur	187	190
Tibia	161	151
Femur + tibia	7	4
Humerus	181	181
Pelvic bones	90	94
Vertebral column	88	94
Head	27	7

The structures named in this table include parts of the skeleton with macroscopically visible tumours. They were all subjected to histologic examination. In the case of the pelvis, the ileum and ischium were examined only unilaterally, in which case the right and left side bones were randomally selected, while the bones from the corresponding side were saved for measurements of activity. The head was divided in the median plane during dissection and examined histologically only when it was suspected of possibly having a tumour.

Methods. The two groups of mice were examined daily both during the mating period and after. In feasible cases animals were killed in an advanced stage of disease to obtain fresh material for the histologic investigations. Moribund animals were killed even in cases in which no tumours had been observed upon inspection. The mice were anaesthetized before death by intraperitoneal injection of 0.15 to 0.30 ml 0.6 % Mebumal® solution, after which blood was obtained from the medial venous *sinus of the eye*. The total

Table 3

Soft tissue tumours in mated and unmated groups

Tumour type		Unmated mice n 97	Mated mice n.97
Squamous cell carcinoma		2	6
Adenoma of the lung		1	5
Adenoma of the ovary		—	2
Pituitary adenoma		—	2
Tumour of the adrenal medulla		1	—
Ependymoma		—	1
Fibrosarcoma		—	1
Leukemia		1	10
Thymoma		—	1
	Total	5 (5 2)	28 (8 9)

leucocyte count was made using a Spencer haemocytometer (from American Optical) The haemoglobin content was examined in a Ljungberg colorimeter and the results, obtained in per cent, were recalculated in gram per 100 ml blood

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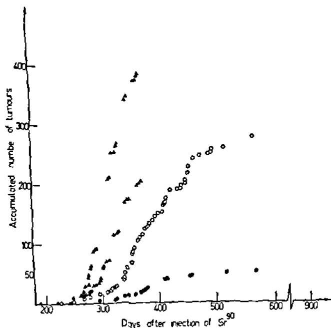


Fig 4 Accumulated number of bone tumours in various bones in relation to time after injection of ^{90}Sr in long bones of unmated mice (△) of mated (○) and in the pelvic bones and spine of unmated mice (▲) of mated (●)

only considering the 60 mice killed at the former time if the mice still living were also included the corresponding value became 2 3 The differences between the two groups are also shown in Fig 3

Tumour localisation For all the skeletal parts examined a significantly higher frequency of tumours existed in the unmated group as shown in Table 4 The most noteworthy finding is the not only numerical but also percentual difference in the number of tumours in the spinal column especially in the lumbar and sacral vertebrae (Table 5 Fig 4) In the unmated group, no less than 112 or 83 6 % of the tumours were localised in the sacral and lumbar vertebrae The corresponding value for the mated group was only 8 or 32 % Furthermore the number of tumours in the pelvis was much lower in the mated group than in the unmated Due to this change in localisation the percentual share of tumours in the long bones had a marked dominance within the mated group

Types of skeletal tumours The classification of tumours was made solely on the basis of the histologic findings The osteoblastic *osteosarcomas* greatly dominated in both groups Of the 627 tumours in the unmated group (Table 6) no

Table 4

Tumour rate per bone — Head and tumours involving two or more bones not included

Site	Mated			Unmated mice		
	Number of bones sectioned	Total number of tumours	Tumours per bone	Number of bones sectioned	Total number of tumours	Tumours per bone
Femur (pairs)	93.5	139	1.48 ± 0.093	95	205	2.16 ± 0.097
Tibia (pairs)	80.5	58	0.72 ± 0.097	75.5	95	1.26 ± 0.106
Femur + tibia (pairs)	*3.5*	*7*	—	*2.0*	*4*	—
Humerus (pairs)	90.5	76	0.84 ± 0.093	90.5	101	1.12 ± 0.094
Long bones (pairs)	268	280	1.04 ± 0.055	263	405	1.54 ± 0.069
Pelvic bones	90	25	0.28 ± 0.072	94	79	0.84 ± 0.098
Vertebral column	88	25	0.28 ± 0.067	94	134	1.43 ± 0.146
Total	446	330	0.73 ± 0.044	451	618	1.37 ± 0.053

ably longer for the mated group than for the unmated, and even the maximum tumour-forming phase appeared later on.

The average length of life for the mated group was 479 ± 11 days, and for the unmated group 386 ± 4 days. It should, however, be kept in mind that these values are approximate, since the animals were killed in agone. However, *in comparison with the normal control material*, with an average life span of 955 ± 26 days, there is a great decrease in length of life within the mated series. The survival, calculated as an average of the time interval between ^{90}Sr injection and sacrifice of the mice, was 399 ± 11 days for the mated group, and 312 ± 4 days for the unmated. The difference is highly significant ($p < 0.001$).

Tumour multiplicity. There was considerable inclination towards occurrence of multiple tumours in both groups investigated. As shown in Fig. 2, this was considerably more so in the unmated group, in which the average number of skeletal tumours per mouse was 6.5 ± 0.32, while for the mated group it was 3.6 ± 0.26, a highly significant difference ($p < 0.001$). The division of the material in Table 1, into classes with respect to the increment in number of tumours per time interval, demonstrates that the total number per mouse in the mated group *maintains* a relatively *constant* level while it perpetually increases in the unmated group. Thus, the number of tumours per mouse in the mated group was 3.6 after 414 days and it was the same after 895 days if

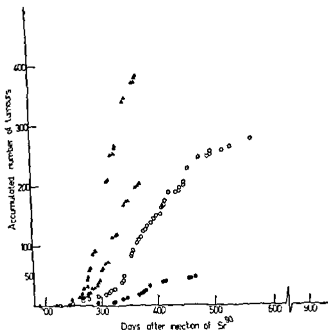


Fig 4 Accumulated number of bone tumours in various bones in relation to time after injection of Sr in long bones of unmated mice (△) of mated (○) and in the pelvic bones and spine of unmated mice (▲) of mated (●)

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Fig 14 Squamous-cell carcinoma oral cavity 458 days after injection of ⁹⁰Sr mated group of mice van Gieson 250

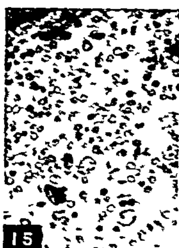


Fig 15 Adenoma of the pituitary 443 days after injection of ⁹⁰Sr mated group of mice H E 250



Fig 16 Magnification of fig 15 Giant cell and endocrine pleomorphism H E 1000



Fig 17 Ependymoma 719 days after injection of ⁹⁰Sr mated group of mice H E 250

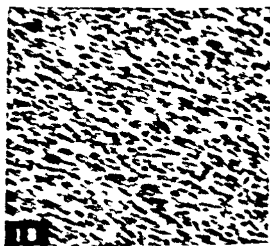


Fig 18 Fibrosarcoma from the extremity 791 days after injection of ⁹⁰Sr mated group of mice van Gieson 250

considered as macroscopic as soon as any part of the tumour mass has penetrated preformed bone and infiltrated the periosteal tissue All foci of proliferation situated intramedullary and containing pleomorphic cell elements have been regarded as microscopic osteosarcomas It may be seen from Fig 19 that the percentage of macroscopic tumours in the long bones is greater in the mated group than in the unmated This is especially evident in the humerus In the vertebral column, however it is quite the contrary The reason

Fig 19 Per cent macroscopical tumours in relation to total number of tumours in different long bones and vertebral column Unmated mice ☐ mated mice ▨

for this as regards the long bones is possibly the longer survival in the mated group permitting a greater number of intramedullary buds to penetrate into the extra osseous tissue This is indicated by the lower incidence of macroscopic tumours in the humerus, especially in the unmated group, since it has been shown that the tumour buds are established later in the humerus than in the femur and tibia (NILSSON 1962) The lower rate of macroscopic tumours in the vertebral column in the mated group seems on the other hand to contradict this assumption It may be however that a very much reduced ^{90}Sr retention as compared with the unmated group could possibly result in a later establishment of tumour buds

It is obvious from this investigation despite the fact that not all bones in every mouse were examined histologically that the number of tumour bearing mice is underestimated especially in mice with a lower ^{90}Sr concentration in their skeletons Thus in this study when only tumours with a macroscopic extent were taken into account the tumour incidence was reduced by 18 % in the mated group as compared with only 2 % in the unmated series This reduction in number of the macroscopic tumours seems to depend upon a later establishment of the buds in the mated group Even if the bone tumours in an early stage of development are autonomous entities, reservations must be made for the possibility that differences in ^{90}Sr concentration may influence the



Fig 14 Squamous cell carcinoma oral cavity 458 days after injection of ^{90}Sr mated group of mice van Gieson × 250

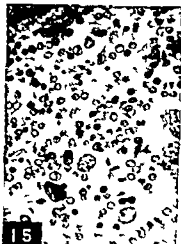


Fig 15 Adenoma of the pituitary 413 days after injection of ^{90}Sr mated group of mice H E × 250



Fig 16 Magnification of fig 18 Giant cell and nucleoli prominent H E × 1000

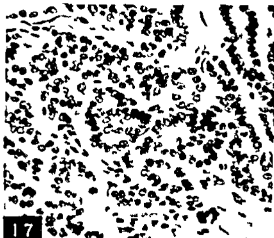


Fig 17 Ependymoma 719 days after injection of ^{90}Sr mated group of mice H E × 250

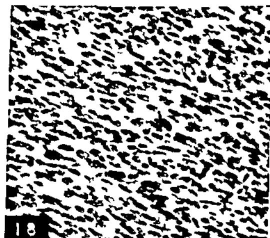


Fig 18 Fibrosarcoma from the eye region 791 days after injection of ^{90}Sr mated group of mice van Gieson × 250

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greater cellularity as well as less developed atrophy and, simultaneously, less apparent megakaryocytopoiesis, granulocytopoiesis and erythropoiesis in the spleens of the mated group This can be attributed to the lower ^{90}Sr retention in the skeleton The more accentuated cell depletion of the marrow within the unmated group makes greater demands upon the compensatory ability of the spleen This may be considered the most important reason for the qualitative and quantitative differences demonstrated histologically

SUMMARY

It was clearly shown from a study of the influence of gestation and lactation on the carcinogenesis of radiostrontium in female mice that this brings about a significant increase in the latency period of bone sarcoma and a similarly significant reduction in the total number of skeletal tumours as compared with the unmated control group A distinct influence on tumour location was also revealed with lower tumour frequency in the lumbar and sacral vertebrae and pelvic bones Damage to the blood and blood forming organs was reduced in the gestating and lactating groups of mice On the other hand the frequency of leukemia increased and to a certain degree also the frequency of tumours in soft tissues

ZUSAMMENFASSUNG

Es wurde gefunden dass die Radiostrontium Karzinogenese in Mausen bei der Gestation und der Laktation so beeinflusst wurde dass das Latenzstadium des Knochensarkoms markant verlangert wurde Auf ahnlicher Weise wurde die Anzahl von Skelett Tumoren im Vergleich mit der ungepaarten Kontrollgruppe reduziert Die Tumor Lokalisation wurde auch deutlich beeinflusst Die Tumor Frequenz in den Lendenwirbeln und Sakralwirbeln sowie in den Beckenknochen wurde vermindert Schaden auf Blut und blutbildende Organe waren geringer in den Gruppen von trachtigen und saugenden Mausen Andererseits wurde die Leukamie Frequenz erhoht und zu einem gewissen Grade auch die Frequenz der Tumoren im Weichgewebe

RÉSUMÉ

Une étude sur l influence de la gestation et de la lactation sur la carcinogénèse par le strontium radioactif chez la souris a clairement démontré que ces états augmentent de façon importante la période de latence du sarcome osseux et diminuent de façon aussi importante le nombre total des tumeurs osseuses par comparaison avec un groupe témoin de souris non accouplées On a constaté aussi une nette influence sur la localisation des tumeurs dont la fréquence est diminuée sur les vertèbres lombaires sacrées et sur les os du bassin Les lésions du sang et des organes hématopoiétiques sont moins importantes dans les groupes de souris en gestation ou en lactation Mais la fréquence des leucoses et dans une certaine mesure celle des tumeurs des parties molles est augmentée

tumour buds to an increased growth rate by direct stimulation or by a depressing effect in the resistance of the host

The occurrence of a considerably higher number of metastases in the mated group, in comparison with the unmated series, can be explained by the fact that a longer survival time provides greater scope for metastasis, even if a possible effect from pregnancy and lactation has to be taken into account Confusion between metastases and tumours is possible, but, with reservation for a changed dissemination pattern for metastasizing in connection with gestation and lactation, this risk does not seem to be important It has been demonstrated in male mice (NILSSON & ULLBERG 1962) that the seeding of metastases primarily occurs in soft tissues before there is any dissemination in the skeleton Apart from a single case seen in the mated group, in which almost all of the soft organs had metastases, it is rather improbable that such a confusion between primary osteosarcoma and metastases could have occurred

Table 3 accounts for the soft tissue tumours which appeared during these investigations, and confirms the observations made by FINKEL (1959) that ^{90}Sr can also induce tumours in epithelial tissue in close contact with bone It is difficult to determine whether hypophyseal adenoma is caused by gestation alone, or results from the combined effects of ^{90}Sr and gestation UPTON & FURTH (1953) suggested that these tumours are probably not induced in the pituitary solely by radiation but that a simultaneous indirect endocrine effect is necessary The latency period was stated to be 17 to 25 months, in this experiment the two tumours appeared somewhat earlier, after 15 and 16 months, respectively ^{90}Sr could be connected with the other types of tumours, since tumours do not usually appear in this strain of mice until considerably higher age It should be mentioned in this connection that during the time in question an osteosarcoma occurred in the control group of 100 CBA males in a mouse when 861 days old, a lymphatic leukemia in another at 805, and a lung adenoma in a third after 875 days

Investigations, made by e g KAPLAN (1950), KIRSCHBAUM (1953) and UPTON & WOLFF (1956), have shown that a hormonal factor is involved in the induction of leukemia However, even if one cannot exclude a hormonal effect, it is probable that the increased leukemia frequency in the mated group depends upon a decreased ^{90}Sr concentration in the mated group compared with that in the unmated series This assumption agrees with preliminary results from which it appears that the leukemia frequency is low with doses of about 0 7 μCi/g bodyweight but increases with doses of between 0 2 to 0 4 μCi/g

The differences observed regarding the blood and blood forming organs between the two groups were a higher leucocyte value in the peripheral blood,

FROM THE DIVISION OF RADIOBIOLOGY (DIRECTOR DOCENT A NELSON), RESEARCH INSTITUTE OF NATIONAL DEFENCE, SUNDBYBERG 4, SWEDEN

EFFECT ON FERTILITY OF CONTINUOUS GAMMA IRRADIATION DURING THE SUCKLING PERIOD IN MICE

by

C RONNBACK

The ovaries of mice are reported to be very sensitive to irradiation with no recovery from the radiation damage There are however variations in the sensitivity depending on the oocyte stage of development at the time of irradiation

Many authors (PETERS 1961 BEAUMONT 1962 EDWARDS & SEARLE 1963) have studied the effects on reproductive performance of a single irradiation dose given at a high dose rate

It was therefore considered of interest to investigate the fertility of female mice which have been exposed to continuous γ irradiation of low dose rate at different stages during infancy This is a continuation of an earlier investigation of γ irradiation of mice in the foetal stage or in the suckling period or both where a dose of 170 R during the whole suckling period was found to make females sterile while the same dose given during the whole foetal stage had no apparent effect (RONNBACK 1965)

Submitted for publication 8 September 1965

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Table 1

Results of uterine analysis in the adult female mice given 100 R during different periods of life — Fertility percentages from cages with at least one female pregnant

Period of treatment	No of analyzed females	Fertility in % of mated females	No of living foetuses	No of dead foetuses	Dead in % of total
1st week	33	12 1	6	1	14 3
2nd »	33	0 0	—	—	—
3rd »	33	69 7	146	11	7 0
Control (not irradiated)	33	84 8	177	8	4 3

Table 2

Fertility in percentage among the tested females from cages in which at least one female mouse was pregnant

Period of treatment (day after birth)	No of analyzed females/dose	γ dose in R				
		Control	25	50	75	100
3 —10	30	63 3	76 7	50 0	10 0	3 3
7 —14	23	65 2	52 2	39 1	21 7	4 3
10 —17	25	72 0	68 0	68 0	36 0	8 0

Materials and Methods The radiation facility consisted of a cesium 137 source of 25 Ci in the front of which four racks accomodated eighteen cages each The distances between the midline of the cages and the source were adjusted in such a way that the dose rate was 3 6, 7 2, 10 8 and 14 4 R/day, respectively, giving an accumulated γ dose of 25 50, 75 and 100 R during one week's irradiation The doses were measured in air by an ionizing chamber (Philips type 37 488/10, HVL 0 07 to 2 mm Cu) placed 1 0 meter above the floor and horizontally and perpendicular to the direction of the beam The ionizing chamber was connected to a Philips Universal Dosimeter of type 37 470 The irradiation was administered continuously, except for a short period each day when the animals were cared for and fed

Females of the same age (about 70 days) from the inbred CBA strain of mice were used in the experiment They were mated to CBA males to produce the litters to be irradiated In the first part of the investigation young females were irradiated with 100 R during their first, second or third week of life In the

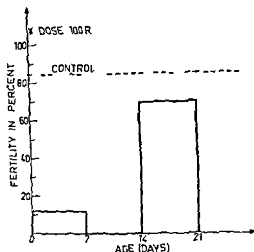


Fig 1 Decrease in fertility after irradiation with 100 R during different age periods

second part 2 week old females were subjected to doses of 25 50 75 and 100 R respectively, given during one week The fertility of these irradiated females was tested by mating them, when they had reached sexual maturity, to untreated males One male was mated to one female from each of the irradiation groups and one non irradiated control female The females were killed and the uterine contents analyzed on the 18th day after mating

Results

Three groups of young mice were exposed to 100 R during their first second and third weeks of life respectively, in the first experiment Young females irradiated during their second week were when mated completely sterile If they were irradiated during one of the other two periods they had decreased fertility compared with that of the control, most marked in the first week group (see Table 1 and Fig 1) This is reflected in the result of the uterine analysis performed on the females (Table 1) A high death rate was observed in the first week group a lower in the third week group but for both of these groups the rate exceeded that of the control group

Further experiments were then performed with females irradiated during their second week of life in order to find any dose relationship during this sensitive period They were subjected to 0 25 50 75 and 100 R, respectively given during the 7th to 14th day after birth When these females had matured they were tested by mating as described above

The radiation sensitivity has also been examined in females irradiated

during their 3rd to 10th day, and in another group during their 10th to 17th day of life They were later tested as above The effect on the fertility is evident in Table 2 as well as in Figs 2 and 3 Fig 2 shows that the most sensitive period occurs during the 7th to 14th day, followed by the period of the 3rd to the 10th Irradiation during the 10th to 17th day produces a period of higher resistance but the fertility is still much lower than in the period between the 14th and 21st day of life (Fig 1)

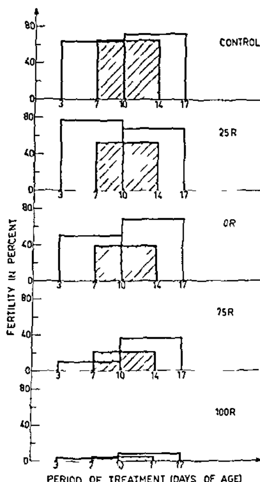


Fig 2 The effect on fertility of different doses given during various age periods

The relationship between dose and fertility is shown in Fig 3 The second week group has a linearity not present in the other two groups, the deviations are probably due to the relatively small number of females analyzed Table 3 and Fig 4 give the litter size, e g the mean number of living foetuses in the pregnant females analyzed There is in overall decrease in litter size with dose, except for the increase between 75 and 100 R in the 3rd to the 10th day group, which however, is due to one single litter consisting of two young

Discussion

The total ability of the animal to reproduce may be used as a criterion of the damage to the ovaries caused by irradiation at birth or soon after birth

Russell & Oakberg (1962) demonstrated that an effect on fertility, which may be long delayed in appearing, may be traced back to cell death within 24 hours after irradiation They found that the number of females having litters as well as litter size, were near normal *until the beginning of a sharp decline* that ended in sterility They suggested that these results might be due to a reduction in the number of oocytes in immature follicle stages

Table 3

Litter size mean number of living foetuses (± standard error) in females irradiated with different doses at different ages — The number of fertile females in each group is given within brackets

Period of treatment (day after birth)	No of analyzed females/dose	Controls (not irradiated)	γ-dose in R 25	50	75	100
3—10	30	5 63 ± 0 53 (19)	5 ₀7 ± 0 27 (23)	3 60 ± 0 31 (15)	1 00 ± 0 00 (3)	2 00 ± — (1)
7—14	23	8 60 ± 0 26 (15)	5 50 ± 0 68 (12)	3 67 ± 0 71 (8)	3 00 ± 0 71 (6)	2 00 ± — (1)
10—17	25	6 11 ± 0 57 (18)	5 8? ± 0 61 (17)	5 47 ± 0 74 (17)	4 00 ± 0 55 (9)	2 50 ± 0 71 (2)

MANDL (1959) irradiated rats with doses between 29 R and 4 400 R and found that the speed with which an individual oocyte disappears seems to be largely independent of the roentgen dose It was demonstrated that the population of oocytes decreases very rapidly during the first 18 hours after irradiation and that the rate of decline after 24 hours is almost negligible

The ovaries of the neo natal female mouse contain small oocytes, they are in early diplotene or still earlier stages (pachytene) (PETERS 1961) Roentgen irradiation on the 21st day with 20 R reduces the number of small oocytes by 99 % the large oocytes on the other hand are not damaged The effect of irradiation at any other time is less severe This radiation sensitivity is regarded by PETERS as immediate cell death With reproductive capacity as a measure of the radiation damage PETERS & LEVY (1963) gave the greatest reduction with irradiation as being on the twenty first day of life where 74 % of the animals were totally sterile

Contrary to PETERS many authors report extreme sensitivity during the second week after birth The sensitivity is increased by a factor of 30 from the time of birth with oocytes in growing follicles to that of oocytes at first metaphase i e about two weeks after birth (MANDL 1963) AUSTIN & HUPP (1964) irradiated rats with 150 R γ rays from ⁶⁰Co at a dose rate of 3 5 R/min and reported no litters from females irradiated on day 7

The fertility was also significantly reduced among those irradiated within the period of the 5th to the 13th day after birth The investigations of RUSSELL RUSSELL, STEELE & PHIPPS (1959) which included continuous γ irradiation of young mice disclosed a rather high resistance of the ovaries of neo natal mice and an extreme sensitivity during the second week OAKBERG (1960)

during their 3rd to 10th day, and in another group during their 10th to 17th day of life They were later tested as above The effect on the fertility is evident in Table 2 as well as in Figs 2 and 3 Fig 2 shows that the most sensitive period occurs during the 7th to 14th day, followed by the period of the 3rd to the 10th Irradiation during the 10th to 17th day produces a period of higher resistance but the fertility is still much lower than in the period between the 14th and 21st day of life (Fig 1)

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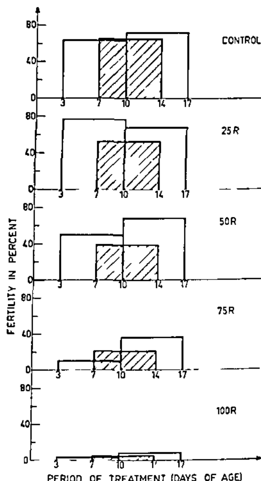


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during the 10th to the 17th day gives a lesser decline in fertility, which rapidly increases during the third week This will be evident from Figs 1 and 2 when comparing the fertility after irradiation with 100 R in the different groups

Fig 3 illustrates the relationship between loss of fertility and dose and Fig 4 gives the same pattern for the litter size In both figures the data from the period of irradiation between the 10th to the 17th day are an indication of a higher fertility and a greater litter size than in the other two periods These two figures again suggest that the duration of the very sensitive period ceases at the end of the second week after birth for the CBA mice

Acknowledgement

The author is indebted to Prof K G Luning for his support of the work

SUMMARY

Female mice were irradiated with γ rays at low dose rates from a cesium source during different periods of their first weeks of life The administration of 100 R during the second week made the females sterile Additional experiment with lower doses carried out during this sensitive period suggested a linear relationship between dose and fertility

ZUSAMMENFASSUNG

Wahrend verschiedenen Perioden wurden junge weibliche Mause in ihren ersten Lebenswochen mit Gamma Strahlen niedriger Intensitat von einer Caesiumquelle bestrahlt Nach Verabreichung von 100 R wahrend der zweiten Lebenswoche wurden die Weibchen steril Weitere Experimente mit kleineren Dosen wahrend dieser kritischen Periode lassen auf ein lineares Verhaltnis zwischen Dosis und Fruchtbarkeit schliessen

RÉSUMÉ

Des souris femelles ont été irradiees par des rayons gamma du césium a faible intensité et pendant diverse périodes des premières semaines de leur vie L administration de 100 R pendant la seconde semaine rend ces femelles stériles Des expériences complémentaires avec des doses plus faibles administrees au cours de cette période de sensibilité font penser qu il y a une relation linéaire entre la dose et la fertilité

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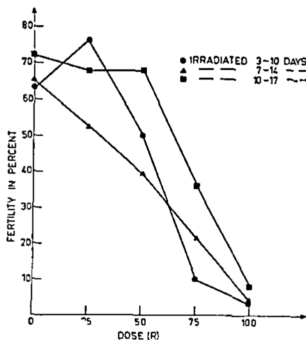


Fig. 3. The relationship between dose and fertility.

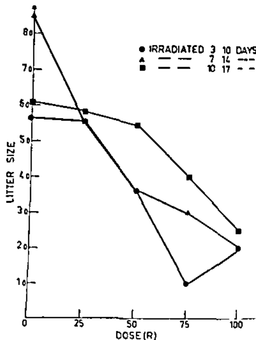


Fig. 4. The relationship between dose and litter size.

made a determination of the LD_{50} of the oocytes of 10 day old mice and found it to be about 9 R.

The results of the present investigation with 100 R gamma rays administered continuously during the first, second or third week, indicate nearly complete sterility of the young females irradiated during the second week, a marked decrease in fertility for those irradiated during the first week, and a degree of fertility not far removed from that of the control for those irradiated during the third week. This is not contradictory to the investigation of RUGH & WOHLFROMM (1964) who found 1-, 2- and 3-week old females to be completely sterilized by exposure to 100 R. Only 1- and 2-week old females were affected by 30 R. That irradiation during the first week does not lead to complete sterility in all females is evident from our Fig. 1. The damage after irradiation during the first week may be attributed to killing of oocytes in pachytene; according to PETERS & BORUM (1961) many of the oocytes are still in that sensitive stage with LD_{50} of 20 R on the day of birth although the proportions may vary between different mouse strains. The resistant phase, with oocytes in early diplotene, may therefore be of short duration, since 96 hours after birth most oocytes have reached the sensitive dictyate stage.

The sensitivity decreases again at the end of the second week, irradiation

during the 10th to the 17th day gives a lesser decline in fertility, which rapidly increases during the third week This will be evident from Figs 1 and 2 when comparing the fertility after irradiation with 100 R in the different groups

Fig 3 illustrates the relationship between loss of fertility and dose and Fig 4 gives the same pattern for the litter size In both figures the data from the period of irradiation between the 10th to the 17th day are an indication of a higher fertility and a greater litter size than in the other two periods These two figures again suggest that the duration of the very sensitive period ceases at the end of the second week after birth for the CBA mice

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FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR ASSOC PROF G HETTINGER), UNIVERSITY OF UMEA SWEDEN

DISPLACEMENT EFFECT OF THIMBLE CHAMBERS EXPOSED TO A PHOTON OR ELECTRON BEAM FROM A BETATRON

by

G HETTINGER, C PETTERSSON and H SVENSSON

Depth doses of high energy photons and electrons from a betatron are often determined with the aid of ionization chambers in a water phantom The ratio between the dose absorbed in water and ionization in the air cavity must then be known however This ratio depends on the radiation energy and thus in the case of electrons on the depth at the point of measurement This ratio has been studied in a number of experimental and theoretical investigations recently performed

When the centre of the thimble chamber is selected as the measurement point the dose/ionization ratio has to be corrected for displacement of phantom material by the air cavity (JOHNS 1961 SPIERS & MEREDITH 1962) SKAGGS (1949) pointed out that the effective measurement point of a cylindrical chamber exposed to electrons from a betatron is just beyond the front wall of the chamber

If no correction for displacement is applied at electron radiation the error in the dose/ionization ratio may amount to more than 20 per cent when a

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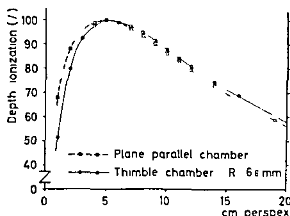


Fig 1 Percentage depth ionization curves measured in perspex exposed to 34 MV roentgen radiation field 8 cm × 8 cm The centre of the thimble chamber was selected as measurement point

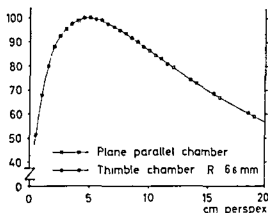


Fig 2 Percentage depth ionization curves measured in perspex exposed to 34 MV roentgen radiation field 8 cm × 8 cm The measurement point was assumed to be in front of the chamber at a distance of 3/4 radius of the air cavity

thimble chamber of 6 mm diameter is used The displacement effect in favourable cases is however masked by the polarization effect At certain field sizes and electron energies this will cause the depth ionization curve approximately to be superimposed upon the depth dose curve

Displacement effects were studied with thimble chambers of different designs and sizes, and the depth ionization values were compared with the response of a plane parallel ionization chamber

Results

The percentage depth ionization curves along the central ray in a 34 MV roentgen beam are shown in Fig 1 *The dotted line corresponds to measurements* with a plane parallel chamber in which the front boundary of the air cavity equals the effective measurement depth The effective measurement points in these ionization measurements were checked by extrapolation, the same depth ionization curve was obtained with different plate distances The solid line corresponds to the response of a large thimble chamber (Philips No 37 480, internal diameter 13 2 mm) its centre representing the measure ment point The axis of the thimble chamber was perpendicular to the direction of the photon beam, a large chamber was chosen in order to elucidate the displacement effect To ensure good geometrical accuracy, the measurements were performed in a perspex phantom but we have found the displacements to be similar when recorded in a water phantom

The displacement between the solid and dotted lines in Fig 1 is almost

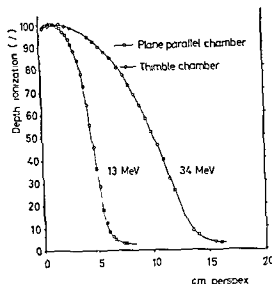


Fig 3 Percentage depth ionization curves measured in perspex exposed to high energy electrons field 8 cm × 8 cm The measurement point of the thimble chamber radius 6 6 mm was assumed to be in front of the chamber centre at a distance of three fourths of the radius

constant The curves coincide (Fig 2) when the measurement point is assumed to be in front of the centre of the thimble chamber at a distance of three fourths of the radius of the air cavity

A corresponding agreement was found with the chambers when exposed to an electron beam of 10—35 MeV (Fig 3) Consistent results were obtained when chambers of different sizes were used i e Siemens Sondenfingerhut kammer and Fingerhutkammer with internal diameters of respectively 6 mm and 16 mm The results seem to be similar to those obtained by DUTREIX & DUTREIX (1965)

Acknowledgement

This work was supported by grants from the Swedish Cancer Society

SUMMARY

A simple correction could be made for the displacement effect of a thimble chamber exposed to high energy photons and electrons from a betatron Good agreement was obtained between depth ionization curves measured with commercial chambers of different sizes

ZUSAMMENFASSUNG

Es wurde gezeigt dass man bei Betatron Bestrahlung mit Photonen und Elektronen von hoher Energie fur die Verschiebungseffekt einer Fingerhut Ionisationsmesskammer einfach korrigieren konnte Gute Übereinstimmung wurde zwischen Tiefenionisationskurven von Messkammern verschiedener Grössen erzeugt

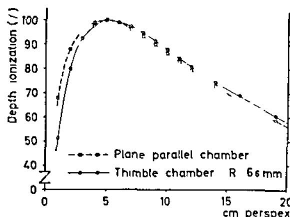


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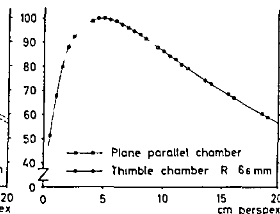


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FROM THE RADIOTHERAPY CLINIC (DIRECTOR PROF S MUSTAKALLIO) UNIVERSITY CENTRAL HOSPITAL HELSINKI FINLAND

ROENTGEN AND TELE COBALT THERAPY OF CANCER OF THE LUNG

by

LARS R HOLSTI

Pulmonary carcinoma is the second commonest form of cancer in Finland According to the Finnish Cancer Registry the number of new cases diagnosed in 1959 was 1 300 i e 25 % of all cases of cancer in males (SAXEN & HAKAMA 1964) The majority of cases are inoperable when diagnosed, and radiotherapy is then the only feasible treatment Roentgen therapy has been employed in Finland for over twenty years (MUSTAKALLIO 1946) not with very good results, however since the 5 year survivals have been only 2 9 % of the cases treated (MUSTAKALLIO 1963) High hopes have therefore been attached to megavoltage therapy

Although a 400 Ci cobalt unit has been available to the Radiotherapy Clinic in Helsinki since 1956 it was not until 1962 that staff became available for individual dose planning During 1956—1961 in a lung cancer series of 69 inoperable cases treated with this cobalt unit without individual planning and isodose charting the 1 year and 3 year survival rates 25 % and 9 % respectively were about the same as those achieved by roentgen treatment in

Presented in part at the XI International Congress of Radiology in Rome September 1965
Submitted for publication 7 February 1966

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Les auteurs ont établi facilement la correction de l effet du déplacement d une chambre dé exposée à des photons et à des électrons de haute énergie émis par un bétatron Ils ont obtenu une bonne correspondance entre les courbes d ionisation en profondeur mesurées avec des chambres commerciales de différentes dimensions

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Table 1

Distribution of total number of cases of cancer of the lung (461 cases) registered 1962—1963

Treatment	Present series	Not included
Roentgen	109	
Treated elsewhere		9
Postoperative		21
Tele cobalt	102	
Split course series		63
Postoperative		13
Betatron photons (33 MeV)		
Split course series		63
Postoperative		12
Photons + pure oxygen		21
Photons + 5 Fluorouracil		16
Untreated	29	
Operated only		3
	240	221

the years 1953—1955, i.e. 29 % and 8 %, respectively (HOLSTI 1965). It was concluded that cobalt itself does not improve the outcome if the technique is the same as in roentgen therapy.

The Radiotherapy Clinic has been housed since 1962 in new premises, and carcinoma of the lung is now treated by a 3 000 Ci tele cobalt unit or a 35 MeV betatron with adequate individual treatment planning. Great expectations are placed in the effect of careful planning on the therapeutic results.

Material. A total of 461 lung cancer cases were referred to the clinic in 1962—1963 (Table 1), 429 cases received radiotherapy, 29 were given no treatment because of their poor condition, and 3 cases that were operated on had no postoperative radiotherapy. Excluded from the present series were the patients who were treated postoperatively, those who received combined 5 fluorouracil and radiotherapy (HOLSTI 1964), and those breathing pure oxygen during treatment (HOLSTI 1966). The cases treated by the split course technique, described by the present author (1966), including those treated by the betatron, were also omitted from the present material.

There remained 109 cases managed by conventional roentgen rays, 102 given tele cobalt, and 29 untreated cases, thus in all 240 cases consisting of 13 women and 227 men. The age range was 28—80, with a mean of 59.3 years.

Table 2

Number of cases and percentages of 1 year and 2 year survivals in relation to spread of cancer and treatments by roentgen and tele-cobalt

Clinical spread	Roentgen treatment			Tele cobalt treatment		
	Number of cases	Per cent survivals		Number of cases	Per cent survivals	
		1 year	2 years		1 year	2 years
No metastases	52	44	12	60	37	8
Intrathoracic spread	27	4	4	24	21	8
Supraclavicular metastases	25	0	0	13	0	0
Distant metastases	5	0	0	5	0	0
	109	22	6	102	26	7

All the cases were histologically or cytologically verified, and the follow-up period for all was a minimum of 2 years No random selection was performed Of the cases that received roentgen therapy 107 were treated in 1962 and only two in 1963 Forty one of the cases given tele cobalt were treated in 1962 and 61 in 1963 all those that had radiotherapy were included in the series however small the dose administered

Methods The factors in the roentgen treatment were 250 kV, 15 mA HVL 1 6 mm Cu with four fields measuring 10 cm × 15 cm or 8 cm × 10 cm, the doses being given by the usual cross fire technique The midline dose was estimated from depth dose tables The most common midline dose was 4 000 to 5 000 R over 6 to 8 weeks *Twelve cases* were treated by the grid technique

Twelve cases in the tele cobalt series were treated by the 400 Ci device and the remainder by the 3 000 Ci unit the FSD was 60 cm Since autumn 1962 individual treatment plans and *isodose* charting have been prepared for each case by means of RP transverse tomography (HOLSTI & EISTOLA 1965) The mediastinum was included in the treatment volume in all the treatments The most common minimum tumour dose has been 5 000 to 6 000 R over 6 to 8 weeks The highest dose was 7 000 R which was given in one case

Treatment was administered 6 times per week in both series Survival was calculated from the start of radiation therapy

Results

The material was divided into four groups on the basis of the clinical spread (Table 2) The first group consisted of the cases in which no metastases were evident at the institution of therapy, the second of cases that were found to

Table 3

Survival times in relation to the different types of tumour in the material

Type of tumour	Roentgen treatment			Tele cobalt treatment		
	Number of cases	Per cent survivals		Number of cases	Per cent survivals	
		1 year	2 years		1 year	2 years
Squamous cell carcinoma	19	33	6	40	35	8
Unclassified carcinoma	7	14	14	13	8	0
Small cell carcinoma including oat cell carcinoma	20	10	5	13	23	8
Anaplastic carcinoma	28	11	4	26	15	4
Adenocarcinoma	4	25	0	4	0	0
Alveolar cell carcinoma	—	—	—	1	0	0
Cytology only	1	100	100	5	40	20

Table 4

Survival times in relation to the doses given

Dose in R	Roentgen treatment			Tele cobalt treatment		
	Number of cases	Per cent survivals		Number of cases	Per cent survivals	
		1 year	2 years		1 year	2 years
< 2500	34	14	6	7	0	0
2500—4000	28	18	7	19	5	0
4000—5000	38	26	8	18	22	11
5000—6000	9	11	0	34	38	12
> 6000	—	—	—	24	37	4

have intrathoracic (mediastinal, hilar, pleural) metastases, the third of those with supraclavicular metastases, and the fourth of cases that already on admission had extrathoracic metastases, *chiefly in the liver and the bones*.

The best results were achieved in the treatment group with no metastases. The table shows, secondly, that both the 1 year and 2 year results were nearly the same with both methods of treatment. The 1 year survival rate with roentgen therapy was 22 % and with tele cobalt therapy 26 %, the 2 year rates being 6 % and 7 %, respectively. None of the cases with supraclavicular metastases survived 1 year. In the group with intrathoracic spread, tele cobalt therapy gave a clearly better result than roentgen therapy.

Table 5

Comparison of treatment results in local squamous cell carcinoma and other carcinoma in the different dosage groups

Dose in R	Roentgen treatment			Tele cobalt treatment		
	Number of cases	Per cent survivals		Number of cases	Per cent survivals	
		1 year	2 years		1 year	2 years
A Squamous cell carcinoma — no metastases						
< 2 500	11	45	18	2	0	0
2 500—4 000	10	40	10	5	0	0
4 000—5 000	10	60	0	4	25	25
5 000—6 000	2	50	0	16	56	6
6 000	—			4	50	25
	33	48	9	31	39	10
B Other carcinomas — no metastases						
< 2 500	3	0	0	2	0	0
2 500—4 000	4	25	25	4	0	0
4 000—5 000	9	33	22	5	20	0
5 000—6 000	3	100	0	9	44	22
> 6 000	—			7	57	0
	19	37	16	27	33	7

The *histologic classification* and the results in the different histologic subgroups are presented in Table 3 Squamous cell carcinoma was the most common in both therapeutic groups and the results were also best for this type of carcinomas Poor results were achieved in the anaplastic carcinomas These observations concur fully with the commonly held view (e g KUTZ 1956 HELLRIEGEL 1963) In small cell carcinomas the results were somewhat better with tele cobalt than with roentgen therapy

The results in the different dosage groups are presented in Table 4 The best results according to both the 1 year and the 2 year survival rates were achieved in roentgen therapy by 4 000 to 5 000 R and in tele cobalt therapy by 5 000 to 6 000 R Higher dosages than these failed to improve the results, while smaller dosages gave poorer results In other words it is not worth exceeding 5 000 R in roentgen and 6 000 R in tele cobalt therapy The results with 5 000 to 6 000 R in tele cobalt therapy were better than with 4 000 to 5 000 R in roentgen therapy

One of the 29 untreated patients survived for over a year The mean survival

Table 6

Comparison between survivals in series treated with roentgen and tele cobalt

Authors and year	Roentgen treatment				Tele cobalt treatment			
	Number of cases	Per cent survivals			Number of cases	Per cent survivals		
		1 yr	2 yrs	3 yrs		1 yr	2 yrs	3 yrs
Smithers 1958	513	21.6	5.6	1.5				
Hellriegel 1963	432	13	4	3				
Bauer et coll. 1965	405	28	7	3.5				
Guttmann 1958					144	33	9	
Kutz 1958					173	24	7	
Beling & Einhorn 1965					138	22	5	
Kuttig et coll. 1962	444	21.6	7.4	3.8	406	28.3	11.2	6.5
Smith et coll. 1964	821	13.3	5	3.6	862	26.4	10.6	8.3
Present series 1966	109	22	6		102	26	7	

time in the untreated group was 3.5 months, in the roentgen treated group 8.1 months and in the tele cobalt group 9.0 months. The results in cases with squamous cell carcinoma and no metastases, grouped according to the different radiation doses, as compared with other cases of cancer without metastases, are given in Table 5. There was no difference in the 2 year survivals in cases with squamous cell carcinoma. The 1 year results were even somewhat better with roentgen therapy.

Discussion

The results obtained in the present material are of the same order of magnitude as those achieved in other materials (see Table 6). It may be concluded that the 1-year and 2 year results with tele cobalt in the present material are not superior to those achieved with conventional roentgen therapy. Careful planning did not improve the results.

Buschke (1957) was of the opinion that supervoltage therapy *would not* significantly change the therapeutic results in the treatment of carcinoma of the lung. Many observations support this view (Sarasin & Chauvet 1959, Garland 1961, Stein et coll. 1962, Hustu & Nickson 1964). It has, however, also been stated that supervoltage therapy, especially tele cobalt, lengthens the life span significantly (Kuttig et coll. 1962, Bauer et coll. 1965) and improves the results (Guttmann 1958, 1961, Kutz 1958). Guttmann (1965) recently reported good results with supervoltage radiotherapy given immediately after exploratory thoracotomy. Other authors have been content with

noting better tolerance to tele cobalt therapy (e g TRIAL & ROZE 1961) No significant difference was evident in the present material in the survival times the mean survival time for the group as a whole was 8 1 months for roentgen treated and 9 0 months for tele cobalt treated cases

As there are no differences in biologic effects between cobalt gamma rays and roentgen rays the most important advantage of tele cobalt treatment is the facility of administering a large dose of irradiation to the tumour HUSTU & NICKSON found no obvious correlation between dose and quality of radiation and survival time On the other hand it has been suggested that higher irradiation doses give better results in cancer of the lung (KUTZ 1958 GUTTMANN 1958 1961) This was true in the present material only for dosages up to 5 000 R in roentgen treatment and 6 000 R in tele cobalt treatment The results were no better with higher dosages

BELING & EINHORN (1965) found that if prognostically poor cases were excluded from their series there was no difference in survival times between the group receiving different irradiation doses However, the proportion of cases registering an improvement increased with the dosage It appears from the present series that the best results in roentgen therapy were achieved by a dosage of 4 000 to 5 000 R and the comparable dosage in tele cobalt therapy was 5 000 to 6 000 R The difference was obviously due to the lower RBE of gamma radiation

With the optimal dosage the results were better for the material as a whole with tele cobalt therapy (Table 4) but no differences were established between roentgen and tele cobalt therapy when only the prognostically favourable cases were compared (Table 5) It seems possible that tele cobalt therapy may increase the survival time slightly in prognostically unfavourable cases such as cases with intrathoracic spread and small cell carcinomas

It is evident from the classification by clinical spread used for the present material that supraclavicular metastases impair the prognosis A few cases with mediastinal involvement survived however for 2 years Pleural metastases are a poor sign prognostically The prognosis was best for squamous cell carcinoma which concurs with the finding of most authors (KUTZ 1956, HELLRIEGEL 1963) On the other hand HUSTU & NICKSON found no correlation between survival time and histology

The results of the present study support the conclusions reached by the present author in a previous paper (HOLSTI 1965) Results with tele cobalt therapy are not much superior to those obtained with roentgen therapy Tele cobalt is nevertheless indicated because less discomfort is experienced during treatment both the general and local reactions are milder However all lung cancer cases cannot be managed in a megavoltage department Conventional roentgen

therapy is still useful in many situations, especially when applied by the grid technique Very good results have been achieved in a selected material with radical roentgen therapy (VESIN 1963) The greatest difficulty about the radio therapy of lung cancer is the ready occurrence of metastases Palliative results were considerably better in cases without metastases on admission Hence, we come back to the old truth early diagnosis is of prime importance in treatment Another chance of improving the therapeutic results today seems to lie in combined operation and radiotherapy, the latter being administered pre operatively (BLOEDORN et coll 1961, MALLAMS et coll 1964)

Acknowledgement

This investigation was supported by a grant from the Finnish State Medical Research Council

SUMMARY

A comparative analysis of 1 year and 2 year results of conventional 250 kV roentgen therapy and with tele cobalt therapy in a material of 240 cases of inoperable histologically verified carcinoma of the lung is presented No great differences were revealed between the two types of radiation but it seems that tele cobalt was superior to roentgen therapy in prognostically unfavourable cases

ZUSAMMENFASSUNG

Die ein und zweijährigen Resultate nach üblicher 250 kV Röntgenbestrahlung und nach Telekobaltbestrahlung in 240 Fällen von inoperablen aber histologisch bestätigten Lungen karzinomen werden berichtet Keine grosse Unterschiede zwischen den beiden Methoden wurden konstatiert aber es erschien lediglich dass in Fällen mit schlechter Prognose die Telekobaltbehandlung wirksammer war

RÉSUMÉ

L auteur présente l étude comparée des résultats à un an et à deux ans de roentgen thérapie classique à 220 kV et de télécobalt thérapie sur une série de 240 cas de cancer du poumon inopérable vérifié histologiquement L auteur n a pas observé de grande différence dans les résultats de ces deux types de radiation mais il semble que télécobalt thérapie est supérieure à roentgen thérapie dans les cas de pronostic défavorable

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FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR ASSOC PROF G HETTINGER), UNIVERSITY OF UMEA, SWEDEN

PHOTOGRAPHIC FILM FOR DETERMINATION OF ISODOSE CURVES FROM BETATRON ELECTRON RADIATION

by

G HETTINGER and H SVENSSON

The clinical use of electron radiation from a betatron necessitates detailed information about the dose distribution in tissue equivalent phantoms for various field sizes and electron energies Due to ageing processes in the betatron, the dose picture may change suddenly, and the isodose curves must be checked regularly In order not to block the betatron too long with such measurements a technique permitting a speedy procedure is of great value

A measurement technique involving the use of photographic films calibrated against ferrous sulphate dosimeters will be described in the present paper The density in film exposed in a polystyrene phantom was found to be essentially linear with the dose at the corresponding points in a water phantom, and geometric scale factors are not necessary for transforming the isodensity curves into isodose curves The film can be quickly evaluated with the aid of an automatic isodensity writer (PETTERSSON, to be published)

MARKUS & PAUL 1953, DUTREIX 1958 LOEVINGER et coll 1961, SPIRA et coll 1962 and BREITLING & SEEGER 1963 have used photographic films for

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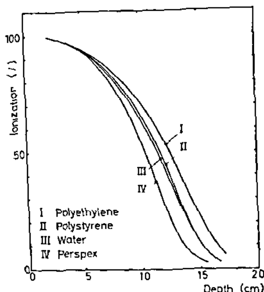
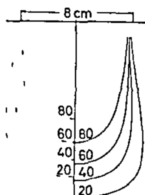


Fig 1 Depth ionization curves obtained for different phantom materials at 32 MeV electron radiation field 8 cm × 10 cm

the determination of isodose curves Systematic errors may however easily arise in the measured dose distributions

At low phantom depths the blackening of the film becomes insufficient if the film is exposed parallel to the radiation beam (MARKUS & PAUL LOEVINGER et coll and BREITLING & SEEGER) The film must be under uniform pressure or else density variations not corresponding to the actual dose distribution within a homogeneous phantom will occur Particular care must be taken when measuring the radiation from a betatron since the output varies both in direction and quality during the first few seconds after switch on Due to its high sensitivity the film may integrate appearances not representative of the dose distribution during an actual treatment which may last for a period longer by a factor of about 10

Film phantom material Phantom materials for high energy electrons have been studied by MARKUS 1956 POHLIT 1960 and LOEVINGER et coll 1961 The latter authors indicated polystyrene as a nearly water equivalent material this equivalence also appears from Fig 1 in which depth ionization curves from measurements in polyethylene, polystyrene water and perspex are presented The retardation of the electrons occur nearly in the same manner in polystyrene as in water which thus may be taken as an indication of the usefulness of this material for film phantoms



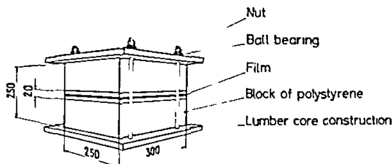


Fig 2 Fig 3

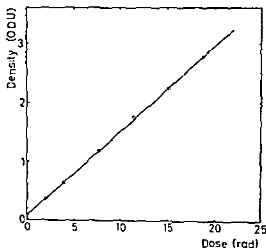
Fig 2 Isodensity curves obtained from a film exposed in a perspex phantom (dotted lines) and isodose curves measured in a water phantom (solid lines) at 28 MeV electron radiation field 8 cm × 10 cm

Fig 3 Schematical view of the film phantom The screws are tightened to reproducible pressure by means of a moment key

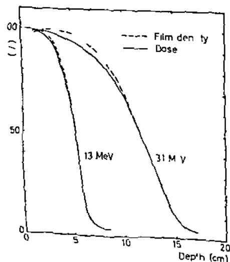
Hitherto, however, perspex has often been used as film phantom material in the measurement of dose distributions from betatron electrons The linear cross sections of electron interactions between 10 and 40 MeV are about 10 % higher in perspex than in water As may be seen from Fig 2, complicated scale corrections have to be applied for both axes in the conversion of the density of the film into isodose curves valid for water Nearly the same linear cross sections are valid in polystyrene and water, and no geometric scale correction is necessary when a polystyrene phantom is used

Technique The design of the film phantom is shown schematically in Fig 3 The photographic film, without envelope, is placed between two polystyrene sheets in a dark room The polystyrene is mixed with latex and is opaque to both daylight and Cerenkov radiation The film magazine is thereafter placed in the polystyrene phantom and the screws are tightened to a reproducible pressure by means of a moment key The film is always exposed parallel to the radiation beam

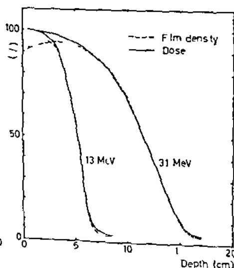
Kodak Microtex film was used in the experiments now reported and the blackening was read on an Ansco MacBeth densitometer (Model 12 A) The high output from the betatron was reduced to a level adapted to the sensitivity of the photographic film and with the aid of a balancing chamber (Pettersson & Hettinger 1965) the inhomogeneity of the radiation field was adjusted in order for it to be the same as that present at higher dose rates



F g 4 Blackening obtained with a Kodak M crotex film expo ed in a polystyrene phantom Development 3 25m temperature 23 0 C Kodak A 3



F g 5 Curves of r l tiv depth bl ken g on fil n (d tted l nes) and d pth dose values (s l d l nes) long the cent al ay



F g 6 R lati e depth blackening urves nor mal zed to th depth dose curve at a depth dose of 90

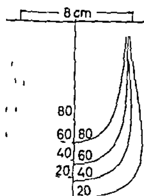


Fig. 2

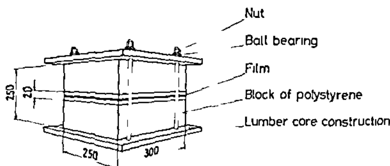


Fig. 3

Fig. 2. Isodensity curves obtained from a film exposed in a perspex phantom (dotted lines) and isodose curves measured in a water phantom (solid lines) at 28 MeV electron radiation. field 8 cm × 10 cm.

Fig. 3. Schematical view of the film phantom. The screws are tightened to reproducible pressure by means of a "moment" key.

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may therefore have to be applied for an ionization chamber placed at the same depth but close to or at the field edges At these points however the dose gradient is high and the uncertainty of dose measurements with ionization chambers will then mainly be due to geometrical errors The result of a comparison between film densities and measurement with calibrated ionization chambers at points beyond the central ray is recorded in Fig 7

Similarly good agreement was obtained for other field sizes and electron energies These results indicate that, in treatment planning photographic films may be used in a polystyrene phantom for the determination of complete isodose curves Relative depth dose and isodose curves for a homogeneous water phantom will be published in more detail in the near future

Acknowledgement

This work was supported by grants from the Swedish Cancer Society

SUMMARY

The use of photographic film exposed in a polystyrene phantom for the determination of depth dose and isodose curves from 10—35 MeV electron radiation is described The technique is especially valuable in connection with an automatic isodensity writer

ZUSAMMENFASSUNG

Zur Bestimmung der Tiefendosis und zur Feststellung von Isodosenkurven bei 10—35 MeV Elektronenstrahlung wurde photographischer Film in einem Polystyrenphantom exponiert Diese Technik ist besonders wertvoll wenn man einen automatischen Isoschwarzungs schreiber zu gebrauchen beabsichtigt

RÉSUMÉ

Les auteurs décrivent l emploi de film photographique exposé dans un fantome en polystyrène pour déterminer la dose en profondeur et les courbes isodoses d un rayonnement d électrons de 10 à 35 MeV Cette technique est particulièrement utile quand on y associe l utilisation d un inscripteur automatique d isodensité

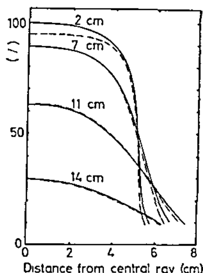


Fig 7 Result of comparison between film blackening and dose at points beyond the central ray at various phantom depths (2 cm 7 cm 11 cm and 14 cm) The percentage depth dose has been plotted against the distance between the central ray and the point of measurement (solid lines) The corresponding density values obtained with film exposed in a polystyrene phantom are represented by the dotted lines

Results

The blackening of the film was found to be linear with the dose up to 3 density units (about 20 rad) (Fig 4) The extrapolated intercept at zero dose was 0 1 The blackening of the film was found to be reproducible to within ± 3 %, but the sensitivity of films from different supplies varied up to 20 %

In Fig 5, a comparison has been made between the relative depth blackening (film density) and the depth dose curves along the central ray The blackening values have been corrected for the extrapolated zero density The depth doses were measured with ferrous sulphate dosimeters in a water phantom The dosimeter solution was kept in polystyrene capsules, the dosimeter readings gave the dose distribution valid for a homogeneous water phantom (PETTERSSON & HETTINGER, to be published)

By normalization of the blackening values in Fig 5 with the depth dose curve at a point corresponding to a depth dose of 90 %, the values obtained for the film phantom are well in agreement with the results obtained with the chemical dosimeters (Fig 6) This was found to be valid also for field sizes and electron energies other than those represented in the diagrams of the present paper

We also investigated the possibility of using a photographic film for the registration of dose distributions beyond the central ray by means of small ionization chambers These were calibrated against ferrous sulphate dosimeters at different electron energies and for various depths in a water phantom The spectral distribution of the electrons at the field limits differs from that along the central ray or in the vicinity of it A different calibration factor

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COBALT 60 TELETHERAPY OF CARCINOMA OF THE BLADDER

by

F EDSMYR F JACOBSSON O DAHL and R WALSTAM

The advantages offered by modern high energy radiation therapy compared with orthovoltage roentgen techniques are frequently discussed and nowadays well known The extent to which these advantages can be utilized to improve the results in the treatment of a particular disease depends on several factors A number of authors have reported considerable improvement by the introduction of high energy radiation techniques in the treatment of carcinoma of the bladder (FRIEDMAN 1959 MORRISON 1960, POOLE WILSON & POINTON 1961 ELLIS 1963 MILLER et coll 1964 VAN DER WERF MESSING 1965)

This paper deals with results obtained at Radiumhemmet since 1957 when cobalt 60 teletherapy was introduced Our treatment techniques have been developed with the aim of delivering a uniform and adequate dose to tissues suspected to be invaded by tumour taking into the consideration the necessity of avoiding intolerable radiation effects in adjacent healthy tissue The clinical classification has been revised according to the recommendations of IUAC (1963)

From Radiumhemmet (Acting Director F Jacobsson) the Urologic Clinic (Director G Giertz) and the Institute of Radiophysics (Acting Director R Walstam) Karolinska Sjukhuset Stockholm Sweden Submitted for publication 28 December 1965

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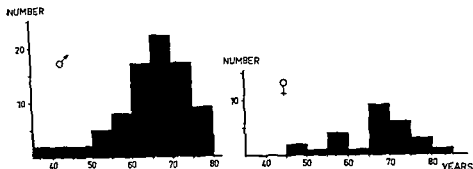


Fig 1 Distribution by sex and age of the case material (for a total of 111 patients)

Table 1

Summary of the results obtained in 111 patients treated at Radiumhemmet during the period July 1957—December 1961

Stage	Years of observation	Number of patients treated	Died free of cancer	Determinate cases	Living	Survival rate
T2	5	—	—	—	—	—
	4	3	—	3	—	0/3
	3	11	—	11	4	4/11
	2	23	1	22	11	11/22
T3	5	9	—	9	1	1/9
	4	20	2	18	5	5/18
	3	3[illegible]	3	29	14	14/29 (48)
	2	38	3	35	19	19/35 (54)
T4	5	11	—	11	2	2/11
	4	21	—	21	4	4/21
	3	46	—	44	7	7/44 (16)
	2	50	—	48	13	13/48 (27)
All patients	5	20	—	20	3	3/20
	4	44	2	42	9	9/42 (21)
	3	89	5	84	25	25/84 (30)
	2	111	6	105	43	43/105 (41)

Material

From 1 July 1957 to 31 May 1964, 272 patients were treated, primarily with external cobalt 60 irradiation This report deals with the first 111 patients, treated up to 31 December 1961, all of whom have been presented earlier (EDSMYR et coll 1964) The distribution by age and sex of the patients is given in the histogram in Fig 1 In all, there were 84 men and 27 women, the mean age of the men being 64 and of the women 67 years

As in all materials of bladder carcinoma, many patients referred for irradiation had already undergone repeated surgical procedures during the preceding months or years According to the system for presentation of results proposed by IUAC (1963), the present material should have been divided into a single group of patients not previously treated (61 patients) and another group previously surgically treated (50 patients), but we have considered it too small to allow such a subdivided presentation of the results One of the patients had been previously irradiated with conventional roentgen rays and had had a recurrence

The clinical staging of the tumours has been made according to the system proposed by IUAC The four tumour stages are defined as follows

T1 Tumour with infiltration of subepithelial connective tissue

- Biopsy evidence of malignancy as demonstrated by infiltration of the subepithelial connective tissue but no evidence of infiltration of muscle
- On bimanual examination a tumour may be palpable but it is soft and freely mobile within the bladder

T2 Tumour with infiltration of superficial muscle

- Biopsy evidence of malignancy but in addition infiltration of superficial layers of muscle
- On bimanual examination induration of the bladder wall may be palpable
- Where the bimanual is indefinite but the biopsy shows infiltration of superficial muscle the category is T2
- Where the biopsy is inadequate and fails to show infiltration of muscle but where the bimanual examination shows a definite induration the category is T2

T3 Tumour with infiltration of deep muscle

- Biopsy evidence of malignancy but in addition infiltration deeply into the muscle wall
- On bimanual examination the tumour can be palpated as a hard or nodular mass but is freely mobile in all directions in the pelvis
- Where the bimanual is indefinite but the biopsy shows infiltration into deep muscle the category is T3
- Where the biopsy evidence of muscle infiltration is indefinite but the bimanual examination shows definite hardness or nodularity the category is T3

T4 Tumour fixed or invading adjoining organs

- Biopsy evidence of malignancy
- On bimanual examination the tumour is fixed to the pelvic wall or invading the prostate vagina or abdominal wall

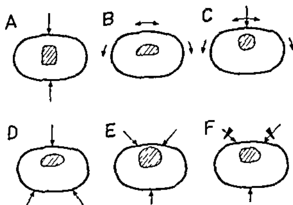


Fig 2 Irradiation techniques suggested for the treatment of tumours of various sizes and sites in the bladder

The *pathologic examinations* of tumour specimens were always made in the same department All tumours in the material have been microscopically verified No sarcomas are included in the material

Treatment

The patients have in general been treated with calculated mean tumour doses of 5 500 to 7 000 rad over 5 to 7 weeks An increasing tendency in recent years has been to give a tumour dose of 900 to 1 000 rad a week when possible (5 day irradiations) A summary of the treatment results is presented in Table I

Irradiation techniques Two kilocurie cobalt 60 units are at present available at Radiumhemmet (HULTBERG et coll 1959 1962) One of these the Gammatron 1 permits the use of moving beam therapy while the other the Eldorado Super G unit, can be used only for fixed field irradiation Both units are equipped with standard filters giving a wedge isodose angle of approximately 45 For modification of the wedge isodose angle in accordance with the requirements in each individual case isodose curves have been calculated for the same portal and different combinations of beams with and without wedge filter (cf SUNDBOM & WALSTAM 1964)

An individual irradiation plan was worked out for each case based on the anatomical outlines of the patient in an horizontal section through the centre of the treatment region The respective sites in this section of the bladder

The classification was always based on the observations made at the first examination. Borderline cases were assigned to the lower stage of classification.

As may be seen from Table I, as many as 50 patients of the 111 in the material (45 %) belong to stage T4. It ought to be mentioned that among these 50 patients one had pulmonary metastases proved at the beginning of treatment, one had peritoneal carcinosis and two others distant gland metastases and skin metastases, respectively. Further, two patients acquired skin metastases and bone metastases, respectively, in the course of the treatment. It goes without saying that among the 50 patients in question, several had malignant growths of the vagina, collum uteri, prostate and urethra.

Especially during the first years of the study, a high percentage of T4 cases were present in the material while the T2 cases were relatively few.

As a special study, in order to obtain information regarding the correspondence between the results of clinical examination and tumour spread in the pelvic cavity, exploratory laparatomy was performed in about 20 patients of the 1963 material. The bladder was not opened but biopsies were performed upon doubtful areas outside the bladder, at the same time certain lymph nodes were extirpated. On the whole, the correspondence seemed to be good. (It was interesting to observe that lymph node metastases were present in some cases classified as stage T2.)

Cystoscopy with biopsy was always carried out. It was performed prior to the radiologic treatment as well as at the subsequent follow-up examinations. The examinations were carried out under spinal anaesthesia in order to facilitate a satisfactory bimanual palpation with complete relaxation of the patient. Thus, the actual bladder volume could also be estimated.

We believe that pre-irradiation surgery should if possible be avoided in all cases of vesical carcinoma. There is always the risk that adhesions occur between the bladder and adjacent organs after a surgical procedure (MORRISON 1960); this may lead to serious damage to the bowel at a subsequent irradiation treatment.

Roentgenologic examinations are always performed before irradiation is started. The recto-sigmoid region is examined roentgenologically to establish the possible presence of adhesions between bladder and bowel or diverticulas of the bowel itself. Urography is performed both before radiotherapy and at all subsequent follow-up examinations. The value of pelvic angiography for the determination of the tumour extension is being investigated. Special studies of vesico-ureteral reflux (EDSMYR & NILSSON 1964, 1965) in relation to tumour localization before and after treatment, and urinary retention during treatment, have been performed.

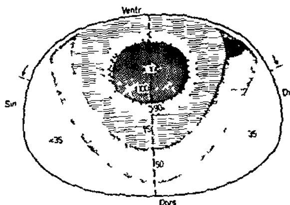


Fig 4 Example of dose distribution obtained with a pendulum irradiation technique

The simple and frequently adopted technique (A) with two opposing beams, gives a relatively heterogeneous and in our opinion unsatisfactory dose distribution even with cobalt 60 radiation (Fig 3) The moving beam technique (B) illustrated in Fig 4 has most frequently been employed for the present material

The aim in dose planning has been to cover the area of the anatomical outline given as tumour area with a homogeneous dose and give as low a dose as possible to regions beyond this area It was possible in most cases to plan the irradiation in a manner to get the actual tumour area enclosed within isodoses representing 94 % to 106 % of the average tumour dose With respect to other factors — such as errors in the absolute measurements of the output from treatment units the three dimensional dose distribution, mobility of organs within the patient possible change of body contour during the treatment and inaccuracy in set up — the dose to the tumour volume was considered to vary within ± 10 % of the calculated average dose

The introduction of new irradiation techniques should naturally be accompanied by more frequent and careful follow up examinations In the course of this study observations made at the repeated patient examinations and improvement of treatment and measurement methods have led to several modifications The more important of these are extension of the margin regions of the tumour area and introduction of a more accurate method for the correction of isodose curves in the event of oblique incidence

Present experience indicates that the tumour area, when the muscle is invaded should include the whole bladder and a margin intended to cover the most

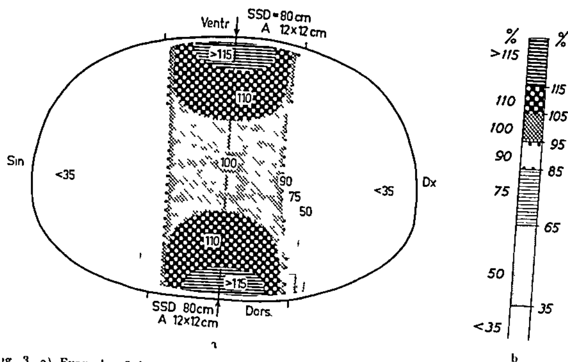


Fig 3 a) Example of dose distribution obtained with the 2 field technique (opposing beams) b) Code of patterns used for the demonstration of the isodose diagrams

the primary tumour, the rectum, and the hip joints were determined by means of clinical and roentgenologic examinations

It was often necessary to use both posterior and anterior fields As the treatment couches at present available in our department are not suitable for irradiation from below, the patient must lie either prone or supine during the irradiation This involves changes in position of the organs as well as of the anatomical outlines These factors are being taken into the consideration when the films are obtained, and the outlines are drawn up for the patients in the same positions as for the irradiations

A schematic illustration of six different treatment techniques, repeatedly employed in the present material, is given in Fig 2 Technique A was used in 7 cases, B in 52, C in 4, D in 32, E in 4, and F in 5 cases, respectively More or less specific individual techniques were used in 7 cases

A colour system is now applied in order to facilitate comparisons between isodose diagrams for different techniques The colours used in practice are represented by patterned areas in our illustrations The levels are standardized to an average tumour dose (100 %), and the patterns are valid as indicated in Fig 3

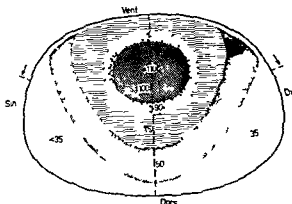


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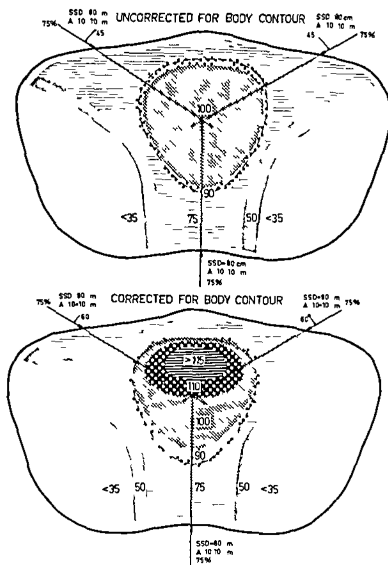


Fig 5 Dose distribution diagrams illustrating the importance of body contour correction The upper diagram shows the distribution calculated for three open fields without taking the body contour into consideration while the lower diagram indicates the distribution really obtained under the conditions stated

probable regional spread of the tumour Correction for oblique incidence of the beam and for body contour has in the last years been made by means of an isodose shift method (DUTREIX et coll 1962, SUNDBOM & WALSTAM 1964) *The importance of such a correction is illustrated in Fig 5*

With the aim of reducing the integral dose an increasing number of patients

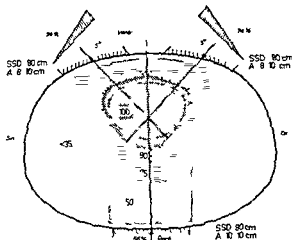


Fig 6 Typical dose distribution obtained with two anterior wedge fields and a direct posterior field

have been treated in recent years by a three field technique using two anterior beams with wedge filters and a direct posterior beam A typical dose distribution obtained with this technique is given in Fig 6 The wedges were in this case applied mainly for correction of the unsuitable dose distribution caused by the oblique incidence of the anterior beams

A study of correlations between physical irradiation conditions and treatment results has been made in a retrospective study of the cases in groups T2 and T3 A recalculation of tumour dose and dose distribution was made for every case according to principles developed during the years covered by this study These involve among others, considerable changes in what was considered to be the tumour area and more accurate correction for obliquely incident beams The study covered 23 patients in group T2, and 34 in group T3 the treatment results of which are given below

	Group T2	*Group T3*
Symptom free > 2 years	6	12
Primary symptom free local recurrences (generally treated with secondary surgery)	9	9
Locally symptom free died of distant metastases	5	0
No primary healing	3	13

It is obvious that tumour doses calculated for tumour areas other than those used in the primary dose planning diverge significantly from those originally

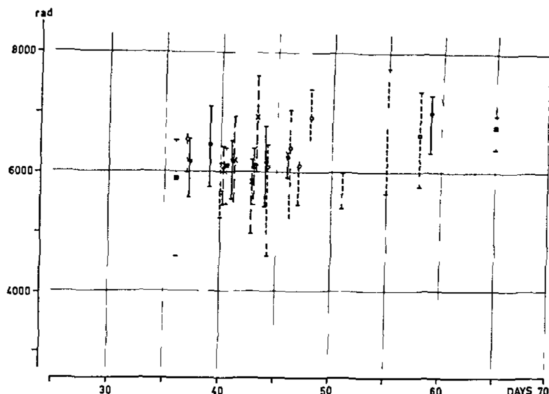


Fig 7 Time dose relationship for the T2 cases ○ Primary symptom free local recurrence × locally symptom free died of distant metastasis ■ no primary healing ● symptom free ⁓ 2 years

calculated The calculated average tumour dose and the maximum and minimum doses within the new tumour area are given in Figs 7 and 8 as functions of the total treatment time A summary of this material is presented in Table 2 It is obvious from the table and the figures that the doses recalculated by the present methods indicate considerably less homogeneous distribution in the tumour area than was originally intended

An attempt has also been made to estimate from the dose distribution diagrams to what extent the regional lymph nodes were included in the area irradiated This was done by two investigators who judged the conditions independently A division into three groups was made, according to whether the regional node chains were considered to have been included in the irradiated area (defined as 75 % of the average tumour dose), whether excluded, or the case was considered doubtful Such factors as the total integral dose and the percentage of the new tumour area receiving more than 110 % or less than 90 %, of the average tumour dose, were also studied

Although the material is small, and the range of dose variations fairly large

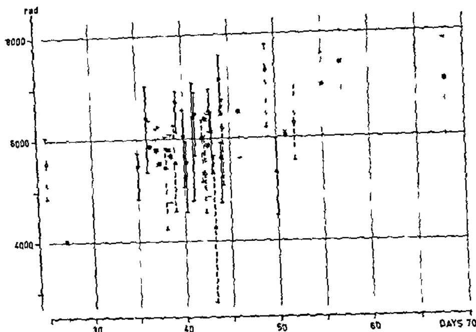


Fig 8 Time dose relation h p fo the T3 cases ○ Primary symptom free local recurrence ■ no primary healing ● symptom free > 2 years

it was considered to be of some interest to summarize the observations made in the investigations

What is to be considered the most suitable treatment technique cannot be determined from this series since the moving beam technique alone was used in a relatively large number of cases The moving beam technique generally implies a somewhat higher integral dose than the three field technique but no signs of unwanted reactions due to this could be observed in the material

In one of the three patients in whom intense rectal radiation reactions were observed, an underestimation of the rectal dose by erroneous correction for the incidence of the beams may have been one of the possible sources of error

No significant correlation between the treatment results and the degree of inclusion in the treatment area of the regional lymph node chains could be demonstrated A summary of the observations is given in Table 3 It is obvious from this table that the number of patients in whom the regional lymph nodes were considered excluded from the tumour area is small but in most of them

there was local recurrence In most of these cases, however, an adequate dose was given only to a small lateral or frontal part of the bladder

The time dose relationship for the treatments in the present material cannot be stated in simple figures, as is often the case with similar series The difficulties may be appreciated from Figs 7 and 8 and Table 2 With respect to the recalculations discussed above it would seem that even in this carefully planned and executed series the divergences in the calculated doses (maximum, average and minimum) are great

Reactions and complications Skin and general reactions have been negligible throughout A few patients exhibited marked signs of cystitis during irradiation Frequency and dysuria, when appearing at all, were generally mild, however Antispasmodics have been used to some extent Some patients had mild diarrhoea *Since 1962, proctoscopic studies have revealed very slight* rectal reactions The prophylactic intrarectal use of prednisolone drugs have proved most valuable

In the material of 111 patients now reported upon, the complications have been comparatively few (8 cases) (7 2 %) They are summarized below in relation to the locations

Bladder (4 cases)

Contracted bladder without known cause	1
Contracted bladder caused by permanent catheter	2
Severe bleeding due to teleangiectases	1
Rectum and sigmoid colon (2 cases) Haemorrhagic sigmoiditis and stricture requiring colostomy	2
Small bowel (1 case) Ileus due to adhesion of ileum to the pelvic wall requiring ileotransversostomy	1
Bone (1 case) Fracture of femoral neck (previous roentgen therapy for bladder tumour)	1

Secondary operations

Special attention has been given *to problems connected with postradiologic* surgery All the patients in the present material secondarily operated upon by different surgical methods at various times after the completion of radiation therapy, are briefly reported in the following (compare with Table 4) (In seven patients, not now reported upon, only a diversion was performed) All the patients had been treated with tumour doses of the order discussed before

Table 2

Summary of physical data obtained in a further study of the cases in groups T2 and T3

	Group T2			Group T3		
	Mean	Min	Max	Mean	Min	Max
Average tumour dose rad	6 300	5 500	7 100	6 000	4 000	7 400
Highest dose within the tumour area (in % of average tumour dose)	107	104	112	110	101	143
Lowest dose within the tumour area (in % of average tumour dose)	88	75	95	84	50	97
Treatment time (days)	46	36	65	43	27	68

Table 3

Summary of the investigation results regarding the dose to the regional lymph nodes

Treatment result	Group T2 — Regional lymph nodes			Group T3 — regional lymph nodes		
	included	doubtful	excluded	included	doubtful	excluded
Symptom free 2 years	4	2	—	10	1	1
Primary symptom free local recurrence	4	2	3	5	1	3
Locally symptom free died of distant metastases	4	1	—	—	—	—
No primary healing	2	1	—	6	1	1

Clinical stage T2 — A Transabdominal surgery

Total cystectomy in a 64 year-old man Recurrence ten months after irradiation No tumour was found on bimanual palpation The bladder was adherent to the left side (the tumour side) and was technically difficult to free The operation had apparently not been radical The microscopic examination disclosed a small superficial recurrent growth not infiltrating the muscle Rupture of sutures in the operation scar which healed secondarily however occurred two weeks postoperatively No other complications occurred

One year later there was bleeding from the urethra Microscopy of material from the prostatic cavity and urethra indicated carcinoma No further treatment was given The patient was alive one year and nine months after operation

Total cystectomy in a 72 year-old man Clinical recurrence one year and two months after irradiation No tumour was palpable Cystectomy and right sigmoidal ureterostomy with cutaneous ureterostomy on left side were performed and no complications occurred The microscopic examination revealed superficial carcinoma of the bladder wall with submucosa but

Table 4

Secondary operations performed in patients with lesions in the three different clinical stages

Clinical stage	A Transabdominal surgery				B Transurethral surgery
	Total number	Postop death*	Total cystectomy	Partial cystectomy	Total number
T2	3	—	2	1	2
T3	4	—	4	—	2
T4	2	1	2	—	1
T2—T4	9	1	8	1	5

* Death postoperatively within one month

muscle not affected The prostate was normal Two months after the operation pyelonephritis occurred and there were difficulties with the cutaneous ureterostoma Left nephrostomy and right nephrectomy were performed The patient died two months later in uremia Sectioning revealed pyelonephritis of the left kidney There was thrombosis of the left renal vein no distal metastases

Partial cystectomy in a 49 year old man Papillomas were revealed at cystoscopy nine months after irradiation No treatment was given Six months later thiotepa was administered locally for nine weeks with 60 mg once a week no improvement Operation was performed one year and nine months *after irradiation sectio alta partial cystectomy and electrocoagulation* The pathologic report indicated a superficial carcinoma not infiltrating the muscle No surgical complications occurred The patient was free from symptoms one year after the operation

Clinical stage T2 — B Transurethral surgery

A 76 year old man Clinically limited recurrence one and half year after irradiation no tumour was palpable Because of the generally poor condition of the patient only transurethral excision followed by coagulation was performed No complications occurred Seven months later there was a further recurrent growth localized near the first one The growth was electrocoagulated The patient died eight months later of bilateral pyelonephritis and carcinoma Autopsy revealed bone metastases and local growth of tumour in the bladder

A 67 year old man Recurrence two years after irradiation No tumour was palpable Only electrocoagulation (twice within an interval of six months) was performed owing to the poor condition of the patient The bladder capacity was unchanged after the operation The patient died from heart failure three months after the last operation Autopsy disclosed bilateral pyelonephritis a growth in the bladder and pulmonary metastases

Clinical stage T3 — A Transabdominal surgery

Cystectomy in a 60 year-old man Residual movable egg sized tumour was disclosed by bimanual palpation and cystectomy was performed No complications occurred no lymph

node metastases were revealed The pathologic report indicated radically extirpated necrotic carcinoma with marked irradiation changes Left cutaneous ureterostomy was performed (From the beginning of the treatment there was no right renal function) The patient was free from symptoms four years after the operation

Cystectomy in a 69 year-old man Residual plum sized tumour was disclosed by bimanual palpation seven months after irradiation Cystectomy was performed without difficulty The pathologic report indicated carcinoma with marked irradiation changes Several lymph node metastases were palpable these were left in place The patient died three months later

Cystectomy in a 55-year-old man There was recurrence two and a half year after irradiation no tumour was palpable Cystectomy was performed The patient was free from symptoms one year later

Cystectomy in a 64 year-old man A residual tumour was disclosed six months after irradiation no tumour was palpable A diversion was first performed without complications and three months later cystectomy without difficulty Slow healing due to wound infection The patient was free from symptoms two years later

Clinical stage T3 — B Transurethral surgery

1 75-year-old woman Recurrence of small growth seven months after irradiation no tumour was palpable Owing to age only electrocoagulation was performed There was a further recurrence three months later and no therapy was given owing to the poor condition of the patient who died two and a half years after the coagulation

4 60 year-old man Clinical recurrence two years and three months after irradiation no tumour was palpable Only superficial coagulation since the growth was considered small No complications occurred and the bladder capacity was unchanged The patient was alive eight months after the operation

Clinical stage T4 — A Transabdominal surgery

Cystectomy in a 51 year-old man Recurrence of growth one year after irradiation plum sized tumour disclosed by bimanual palpation Cystectomy was performed (*ileum bladder*) No complications occurred The pathologic report indicated carcinoma of the bladder and prostate not involved no lymph node metastases One year later there was bleeding from the urethra Specimen from the operation cavity disclosed carcinoma No treatment was given The patient died one month later from coronary thrombosis autopsy indicated bilateral pyelonephritis and carcinoma only in the operation cavity with no distal metastases

Cystectomy in a 54 year-old man Bimanual palpation revealed an egg sized tumour partly adherent to the right pelvic wall eight months after irradiation Diversion was done and one month later cystectomy No lymph node metastases were palpable The operation was not considered radical as the bladder was fixed to the pelvic wall postoperative fistula The patient died one year after cystectomy

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Clinical stage T3 — A Transabdominal surgery

Cystectomy in a 60 year old man Residual movable egg sized tumour was disclosed by bimanual palpation and cystectomy was performed No complications occurred no lymph

Table 5

Response to treatment of primary tumour according to stage of disease

Stage	Number of patients	No tumour seen at cystoscopy				Little or no response		Death without cystoscopy
		At 4 months		At 6 months				
		Number	%	Number	%	Number	%	Number
T2	23	19	83	18	78	3	13	1
T3	38	22	58	22	58	13	34	3
T4	50	13	26	13	26	37	74	—

Table 6

Local recurrence of growth after radiotherapy

Stage	Number of patients	Tumour recurrence		Time after irradiation
		No	%	
T2	18	9	50	7 7 7 9 9 11 16 18 24 months
T3		9	41	7 9 9 9 11 11 13 15 24 months
T4	13	4	31	8 12 20 29 months

and so located that there is no difficulty in performing an excision with a safe margin and if there is no evidence of high malignancy All tumours in stage T3 and T4 are primarily irradiated

The patients have generally well tolerated a calculated tumour dose of 5 500 to 7 000 rad over 5 to 7 weeks

Present experience suggests that the tumour area in all cases in which the muscle is invaded should include the whole bladder and the margin selected so as to cover the most probable spread of the tumour

A thorough infection prophylaxis which should be carried out before, during and after irradiation is of paramount importance for a successful treatment Intravesical manipulation should be avoided, and weekly bacteriologic examinations of the urine must be performed Whenever infection appears this should be intensively treated Patients with vesical carcinoma often have a diminished bladder volume the impression has been gained that it is unwise to irradiate when the bladder volume is less than 100 ml

Clinical stage T4 — B Transurethral surgery

A 74 year old man Residual hazelnut sized tumour present one year after irradiation no tumour was palpable Owing to the age of the patient only transurethral excision was per formed No complications and no change in the bladder cavity occurred The patient was alive one year and eight months later

Follow up examinations A regular control of the patients after completion of the treatment was found to be of the utmost clinical importance The radio therapist should examine the patient at least every fortnight during the first two months following irradiation A general examination including cystoscopy under spinal anesthesia and urography has been carried out every second month during the first year By these follow up examinations it has been possible to judge the response of the primary tumour The response to treatment of the primary tumour, observed by cystoscopy four and six months, respectively, after completion of the irradiation, is recorded in Table 5

In some of the patients, little or no radiation response of the primary tumour was observed In others, the tumour had disappeared at cystoscopy after irra diation, at several controls, but reappeared later As may be seen from Table 6 all these recurrences appeared within three years after irradiation A remark able difference between the response of the lesions in the different stages was apparent

Distant metastases In 28 patients, from whom sections were obtained it was found that the following organs were invaded by carcinoma in 11 patients the liver, in 8 the lungs, in 8 the bones, in 8 the lymph nodes, in 2 the skin, and in one patient, finally, the kidney and the suprarenal organs were involved In some of these patients, more than one organ was invaded

Discussion

Close collaboration between the different specialists is of the utmost impor tance in the treatment of carcinoma of the bladder The selection of patients for cobalt 60 teletherapy was made by a team of urologists, radiotherapists and roentgenologists, who also co operated in the follow up of all the patients

The following rules for treating bladder carcinomas are adopted For carcino mas in stage T1 (submucosal tumours) surgical therapy is usually recommend ed Radiation therapy may be indicated when the tumours are found micro scopically to be highly malignant or if they are so extensive that the only alter native is total cystectomy

Tumours with superficial muscle involvement (stage T2) are usually irra diated Surgery may however be considered if the tumour is small enough

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A thorough infection prophylaxis which should be carried out before during and after irradiation is of paramount importance for a successful treatment Intravesical manipulation should be avoided and weekly bacteriologic examinations of the urine must be performed Whenever infection appears this should be intensively treated Patients with vesical carcinoma often have a diminished bladder volume, the impression has been gained that it is unwise to irradiate when the bladder volume is less than 100 ml

The material is still too small, and the patients have been followed up for too short a time, to enable any definite conclusions Local recurrences seem to appear within three years after treatment, however The results with respect to the local effect of irradiation after three years are therefore of value

A secondary operation may be considered in patients with little or no response to radiation A rather high postoperative mortality must be anticipated in cystectomy patients This has, however, to be weighed against the chance of cure after surgery in some patients Total cystectomy after full dose irradiation with cobalt has been performed successfully in three stage T3 patients of the present material The authors feel that the patient must be under 70 years of age and in good general condition to be considered a candidate for total cystectomy

A general examination including cystoscopy under spinal anesthesia and urography has been carried out every second month during the first year, as previously stated The first cystoscopy after treatment should be made at about 4 months Later on, cystoscopy should be performed every second month during the first year in order to be able to operate upon patients not responding to the primary treatment

SUMMARY

One hundred and eleven patients have been treated by telecobalt irradiation for vesical carcinoma After full external irradiation with a tumour dose of 5 500 to 7 000 rad fourteen patients were subjected to operation The survival rates and complications are reported The investigation suggests that high energy therapy is the method of choice in advanced vesical carcinoma

ZUSAMMENFASSUNG

Telekobaltbestrahlung wurde an 111 Patienten mit Blasen Karzinom vorgenommen Nach Telekobaltbestrahlung mit einer Tumordosis von 5 500 bis 7 000 rad wurden 11 Patienten einer Operation unterzogen Die Operationsresultate und die Komplikationen werden beschrieben Als Resultat der Nachforschungen erscheint es dass hochenergetische Bestrahlung die beste Behandlungsmethode ist

RÉSUMÉ

Cent onze malades atteints de cancer de la vessie ont été traités par télécobalt thérapie Quatorze malades ont été opérés après irradiation externe donnant une dose à la tumeur de 5 500 à 7 000 rad Les auteurs indiquent le taux de survie et les complications ils pensent que le traitement par radiation de haute énergie est la méthode de choix pour le cancer avancé de la vessie

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FROM THE CHRISTIE HOSPITAL AND HOLT RADIUM INSTITUTE, MANCHESTER, ENGLAND

PROGNOSIS IN EXTRA-ABDOMINAL NEUROBLASTOMA

by

FRANCIS KELLY

Neuroblastoma is one of the commonest forms of childhood malignancy and it has a sinister reputation because of the rapid development of metastases. A series of 36 cases, treated at our hospital in the decade 1950—1959 has been reviewed and forms the subject of the present paper. Evidence of metastases were present as follows: in 22 cases when first seen, 4 cases developed metastases in hospital, and 3 cases developed metastases within 3 months.

Parents of children with malignant disease are usually very anxious to be given an exact prognosis, and it is helpful to them if a more optimistic outcome can be reasonably predicted. This can be done in cases of neuroblastoma if the tumour arises in an extra-abdominal site.

In the present material, 26 cases had a primary intra-abdominal tumour, and in 9 cases the tumour arose in an extra-abdominal site. One case presented with generalised disease and the site of the primary lesion could not be stated accurately. The sites of the extra-abdominal tumours were extradural in 4 cases, extradural and pelvic in one case, pelvic in 2 cases, and were present in the thorax in one case and in the neck in one case.

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Table

Cases of extra abdominal neuroblastoma

No	Case	Age at onset	Sex	Site	Survival	Length of survival
1		5 yrs	M	Extradural	Died	4 months
2	Case 1	10 yrs	F	Extradural	Alive	8 years
3	Case 5	1 1/2 yrs	F	Extradural	Died	3 1/4 years
4		14 yrs	M	Extradural	Died	7 months
5		12 yrs	M	Pelvis and Extradural	Died	3 months
6		6 yrs	M	Pelvis	Died	2 years 10 months
7	Case 2	7 mths	M	Pelvis	Alive	6 years
8	Case 3	6 mths	M	Thorax	Alive	6 1/2 years
9	Case 4	1 1/4 yrs	M	Neck	Alive	6 years

Biopsy material was obtained in all the cases for histologic examination, and the diagnosis was confirmed by the Pathologists Panel of the Manchester Children s Tumour Registry No case had a full radical surgical excision with removal of all tumour tissue Irradiation therefore was the definitive treatment and when the disease was localised an attempt was made to administer a course of deep roentgen ray therapy in radical dosage for the volume which had to be contained in the treatment fields In nearly all the cases conventional machines at 250 to 300 kV were used as the increased percentage depth dose obtainable by the use of supervoltage apparatus was not required in these thin patients A regional bath type treatment was prescribed in most cases and a tumour dose of 2 500 to 3 000 R in 5 to 6 weeks was given

The 5 year survival rates for all the 36 cases were as follows of 22 males 19 died and 3 were alive of 14 females 10 died and 4 were alive

Of the nine cases of extra abdominal primaries four patients are alive and five are dead One female child died at the age of 4 years 9 months from bronchopneumonia and pyelonephritis She had been treated for a primary neuroblastoma of the extradural space at the age of 1 year 6 months and post mortem examination showed that there was no recurrence of the treated tumour (see Table)

A brief summary of the histories of the cured cases is given in the following case reports

Case reports

Case 1. Female child, aged 10 years, developed a lump and pain in the left hip. At myelography a block at the level of LV5 was seen. At laminectomy an extradural tumour of 5 cm length was exposed and as much as possible of the tumour was removed. It was confirmed histologically to be a neuroblastoma.

A regional lower abdominal roentgen treatment was given with a dose of 3000 R in 33 days. The patient has been free of disease since. She is now 17 years old but her secondary sex characteristics are not developed and she has no menses.

Case 2. Male infant, aged 7 months, developed constipation, vomiting and retention of urine. At laparotomy he was found to have a mass originating in the retroperitoneal tissues of the pelvis and extending up to the umbilicus. Biopsy only was performed.

The patient was treated by abdominal regional irradiation to a mid-plane dose of 2 000 R in 29 days; an extra dose of 500 R over six days was given to the pelvis. He is alive and well at 5 years of age.

Case 3. Male infant, aged 6 months, developed rapid respirations and on chest examination was found to have a mass in the posterior mediastinum. At thoracotomy a cystic mass the size of a tangerine was present in the costovertebral angle DV 7—10. The mass was extrapleural and adherent to the ribs; it was removed as far as possible.

A regional irradiation was given with a dose of 2 500 R in 38 days. The child is alive and well at six years of age.

Case 4. Male infant, aged 1 year 3 months. A lump which grew steadily for one year was found to be present in the left side of the neck. At operation a mass the size of a grapefruit was excised. The tumour was incompletely encapsulated. Histologic examination confirmed the diagnosis of neuroblastoma with no suggestion of differentiation to ganglioneuroma. When seen by the radiotherapist the child was described as having two small masses beneath a well healed scar. A Horner's syndrome had developed postoperatively.

The patient was given a trunk bridge treatment (FASSON et coll. 1957) to the head and neck with a central dose of 2 500 R in 24 days. He is now alive and well at 6 years of age but has tooth decay and the Horner's syndrome is still present.

Case 5. This case of intercurrent death from bronchopneumonia and pyelonephritis previously mentioned may well be included among the cured cases. She had no recurrence of her neuroblastoma of the extradural space 3 years and 3 months after the roentgen treatment.

Discussion

Neuroblastoma is a peculiar tumour in many respects. Although it is a tumour of nerve tissue, no cases have ever been described in the central nervous system. The exact site of origin is often indefinite, even within the abdomen, and extra-abdominal primaries are quite common, i.e. 9 out of 36 cases (25 %). The

prognosis is undoubtedly better in these cases Five (55 %) had been cured of their disease 3 years after treatment

It is interesting to speculate on the possible reasons for the better prognosis in the extra abdominal types It is true that earlier diagnosis is more likely because the tumours occur in sites where physiological functions are more quickly disturbed and the patient is brought early for medical attention But even where the diagnosis has been delayed (Case 4) cure can still be obtained This raises the question of the factors involved in dissemination of the disease with clinical appearance of metastases shortly after diagnosis The extra abdominal types do not show this tendency

This embryonic tumour is highly peculiar in its response to treatment Regression may be spontaneous, or may occur because of haemorrhage into the tumour It may also occur after incomplete surgery, radiation therapy, Cooley s toxins nitrogen mustard antimetabolites steroids or vitamin B12 therapy The mode of action of any of these agents is completely unknown Maturation of the tumour into a benign ganglioneuroma may occur and it is likely that the processes of regression and maturation are quite distinct and possibly unrelated It is possible that the child s defences are capable of being stimulated by a variety of agents and that the defence mechanism may be more efficient in the embryological stage of its existence Four of these five cured patients were under 18 months old when they were treated

Acknowledgements

I wish to acknowledge the work of the paediatricians neurosurgeons and radiotherapists of the Manchester Region who treated the cases that are discussed and described in this paper

SUMMARY

The prognosis of extra abdominal neuroblastoma is good The treatment of choice is radical roentgen therapy A series of nine cases is discussed and five case reports are given Four patients are still alive after three years

ZUSAMMENFASSUNG

In Fallen von extra abdominalen Neuroblastomen kann eine gute Prognose vorgesehen werden Radikale Radiotherapie ist die beste Behandlungsmethode Neun Falle werden diskutiert und in 5 Fallen werden kurze Berichte gegeben Vier Patienten sind noch am Leben nach drei Jahren

RÉSUMÉ

Le pronostic du neuroblastome extra abdominal est bon et son traitement de choix est la roentgenthérapie radicale L'auteur présente une série de 9 cas dont 4 sont encore en vie après trois ans

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FROM THE DEPARTMENTS OF RADIATION PHYSICS AND RADIOTHERAPY, UNIVERSITY OF LUND SWEDEN

TECHNIQUE AND DOSE DISTRIBUTION FOR TREATMENT OF CANCER OF THE LARYNX WITH A CESIUM UNIT

by

ULLA BRITA NORDBERG and HANS OLIVECRONA

Carcinoma of the larynx with the growth limited to the vocal cords is usually treated by irradiation An extensive review of the use of conventional roentgen irradiation of intrinsic laryngeal tumours was published by NIELSEN & STRANDBERG (1942) JACOBSSON (1952) employed high energy radiation from a teleradium apparatus Since then this type of tumour has been treated with high energy radiation from various types of apparatus TUDWAY & FREUNDLICH (1960) and HORNYKIEWYTSCH (1961) used cobalt 60 radiation with two or three ports of entry and wedge filters Treatment with the same radiation quality using one field two opposing fields or rotation techniques has been reported by WANG & SCHULZ (1963) and by FLETCHER & KLEIN (1964) High energy radiation as roentgen rays from a 4 MeV generator and electrons from a 42 MeV betatron was applied by GREENE (1964) who employed respectively wedge filter and bolus The adaptation of a decacurie cobalt 60 apparatus for laryngeal treatment with two fields inclined

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RÉSUMÉ

Le pronostic du neuroblastome extra abdominal est bon et son traitement de choix est la roentgenthérapie radicale L auteur présente une série de 9 cas dont 4 sont encore en vie après trois ans

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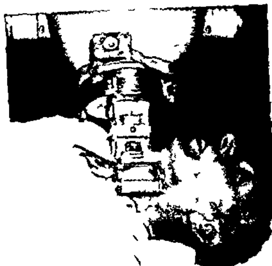


Fig 2 The special collimator adapted to the unit and patient in treatment position

pound construction The total tumour dose has been approximately 6 000 rad over 30 days

The combined use of a neck support and the special collimator serves to achieve adequate treatment conditions and to immobilize the patient (Fig 2) The set up for treatment is easily obtained by adjusting the collimator until the guide point on the skin lies at the centre of the bar

The treatment has been planned from two symmetrical portals with an inclination angle of about 90 and the straight line distance between the field centres has been about 50 mm These two parameters may be varied according to individual requirements

Before and during the treatment and in order to study the influence on skin reactions of a lowering of the surface temperature of the skin a stream of cold air has been forced through the collimator A skin temperature of about , C has been used

Dose distribution Because of the superficiality of the tissues to be irradiated and the small intersectional area of the neck the isodose distribution must be determined separately for different wedges distances and beam inclinations

The dose distribution in a plane through the larynx was determined with small condenser chambers in a tissue equivalent phantom of normal size and with an air cavity corresponding to the trachea A study has been made of the

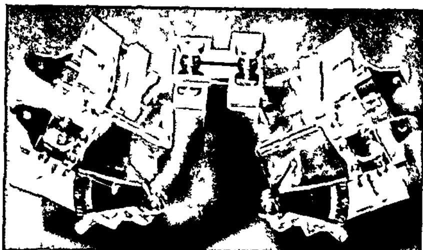


Fig. 1. A special collimator fitting the standard collimator field 4 cm × 4 cm at 15 cm FSD.

at 90° was described by LINDELL & WALSTAM (1956), this technique was later improved by addition of a wedge filter (WALSTAM 1965).

In this paper, a technique for treatment of tumours of the vocal cords by means of a cesium 137 unit is described and the resultant dose distribution is presented.

Technique. In order to obtain an optimal configuration of the neck in relation to the chest and chin a neck support is selected individually to suit each patient. In this position, a sketch is made of the contour of the neck at the level of the larynx and a lateral roentgenogram is obtained. The point where the plane through the vocal cords intersects the median plane is marked out on the skin to serve as a guide during treatment. The position and the length of the vocal cords are determined from the roentgenogram and transferred to the sketch, full allowance being made for the enlargement. The limits of the tumour and the positions of the spine and spinal cord are defined and indicated.

The treatment is administered with a Picker cesium unit provided with a specially made collimator consisting of two identical parts joined by a bar (Fig. 1). This bar is so constructed that the distance between the entrance points of the two fields can easily be adjusted. The special collimator fits to the standard collimator and has a holder for wedges and a nozzle for connection to a compressed air cylinder. The field size on the skin is 4 cm × 5 cm and the source skin distance 20 cm. Three different types of wedges are used, two with isodose angles of about 30° and 40° and a third representing a com



Fig 2 The special collimator adapted to the unit and patient in treatment position

pound construction The total tumour dose has been approximately 6 000 rad over 30 days

The combined use of a neck support and the special collimator serves to achieve adequate treatment conditions and to immobilize the patient (Fig 2) The set up for treatment is easily obtained by adjusting the collimator until the guide point on the skin lies at the centre of the bar

The treatment has been planned from two symmetrical portals with an inclination angle of about 90 and the straight line distance between the field centres has been about 50 mm These two parameters may be varied according to individual requirements

Before and during the treatment and in order to study the influence on skin reactions of a lowering of the surface temperature of the skin a stream of cold air has been forced through the collimator A skin temperature of about 7 C has been used

Dose distribution Because of the superficiality of the tissues to be irradiated and the small intersectional area of the neck the isodose distribution must be determined separately for different wedges distances and beam inclinations

The dose distribution in a plane through the larynx was determined with small condenser chambers in a tissue equivalent phantom of normal size and with an air cavity corresponding to the trachea A study has been made of the

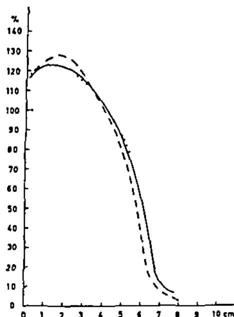


Fig 3 Curves showing the dose variation along the symmetrical line of dose distribution with different distances between the entrance points 46 mm (– – – –) 50 mm (————) and 54 mm ( ) Compound wedges and an inclination of 90 between the beams were used

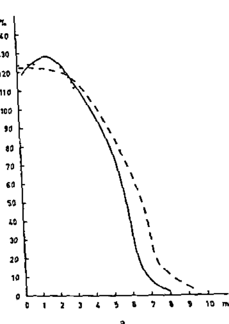
dose distributions obtained with different inclination angles, field distances and wedge filters The values were normalized to 100 % of the dose at each entrance field without use of wedges

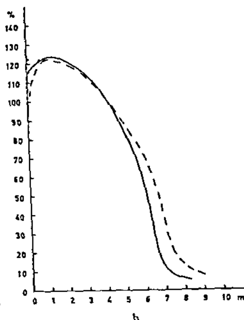
The variation in dose at distances of 46 mm, 50 mm, and 54 mm respectively, along the symmetrical line of dose distribution, and with constant inclination angle between the entrance points, is indicated in Fig 3 The compound wedge was used As could be expected the maximum dose reached a higher value and the downward slope of the curve was steeper for the shortest distance, *while the greatest distance was represented by the lowest value for the* dose maximum and a less steep curve The three curves intersect at a depth of 3 5 cm

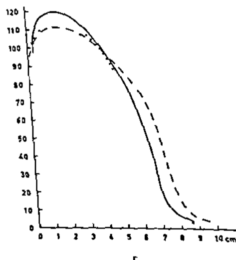
The diagrams in Fig 4, on the other hand, show the dose variation, with a varying angle between the beam directions, at constant distances of 46 mm, 50 mm, and 54 mm, respectively, between the entrance points, using the same wedge as in Fig 3 As may be seen from all the three diagrams of Fig 4, the dose decreases rapidly with increasing angle between the beams

The complete dose distribution corresponding to the curves in the diagram of Fig 4b is presented in Fig 5 The three dose distributions have in common a region of uniform dose concentrated around the laryngeal portion of the neck, whereas the dose to the other part of the neck is quite low

An analysis of all the measurements has enabled the selection of an adequate distance *between the beams in relation to the position of the* lesion to be treated After determination of the distance between the two entrance points, the angle







F g 4 Do e variation along the symmetrical l ne of dose d stribut on with d fferent distances be tween the entrance po nts and varying degree of i cl nation between the beam d ections D s- tance between the entrance po nts 46 mm n (a) 50 mm in (b) and 54 mm in (c) The ncl nation was 80 for curves (— — — —) 90 for curves (————) and 100 fo curves ( )

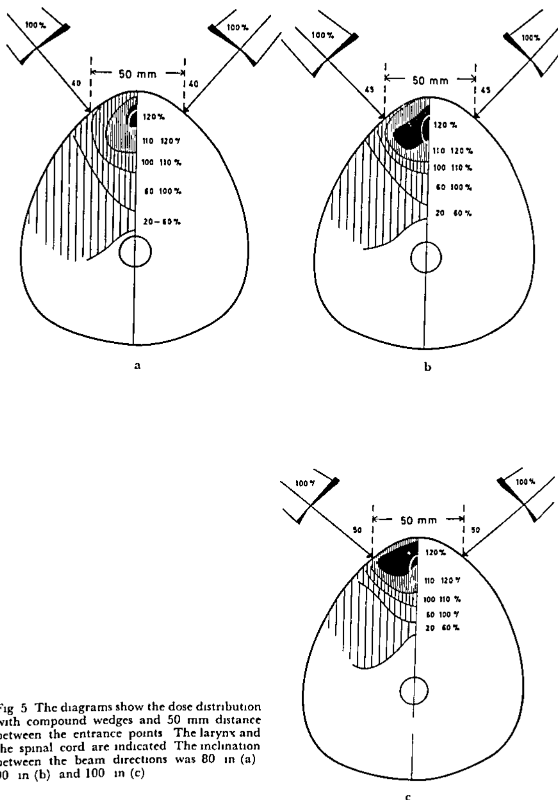


Fig 5 The diagrams show the dose distribution with compound wedges and 50 mm distance between the entrance points The larynx and the spinal cord are indicated The inclination between the beam directions was 80 in (a) 90 in (b) and 100 in (c)

may be altered to suit the contour of the patient s neck A distance of 46 mm between the entrance points produces a uniform dose of 120 $\pm$ 10 % within 0 to 3 5 cm for 50 mm the dose is 115 $\pm$ 10 % within the same limits and for 54 mm it is 110 $\pm$ 10 % within 0 5 to 4 0 cm along the symmetrical line

Discussion

The radiologic treatment of carcinoma of the larynx means irradiation of a lesion of limited extension surrounded by cartilage and there is no need of a large depth dose since the tumour is in a superficial position The depth dose of conventional roentgen quality is sufficient but this radiation quality is not quite suitable because the energy absorption is then greater in cartilage than in soft tissue With high energy radiation this undesired effect can be avoided but the commonly applied sources such as accelerators and teleisotope units usually give a too large depth dose By the use of a cesium unit for short distance treatment the dose to the cartilage is not increased and the short source skin distance leads to a relatively small depth dose The energy of the radiation from a cesium source also provides the possibility of obtaining a good collimation of the beam with applicators sufficiently small in size as not to impede the treatment Also because of the short treatment distance, a satisfactory immobilization of the patient can be achieved without use of any special casts or moulds immobilization of the patients is highly desirable when treating a region of so limited extension as the vocal cords Positioning as well as reproducibility can be easily achieved with the simple arrangement employed The treatment technique can be individualized by variation of distance angle and wedge to obtain the depth and width of the dose maximum that conforms to the actual tumour region

With cesium radiation of 0 66 MeV energy the build up region becomes small and the skin dose is therefore comparatively high The skin reactions have however been moderate and only slightly disturbing for the patients At about two months after the end of the treatment the skin has been soft and slightly pigmented Wet dermatitis has sometimes occurred within circumscribed areas particularly in skin folds We have therefore studied the possibility of reducing the skin reactions by local cooling of the irradiation area LIEBNER et coll (1962) have reported that a good sparing effect was obtained by chilling the skin with cold water during the irradiation In the present series and to enable comparison we have only chilled the right side during each treatment The treatment reaction has been slightly milder on the chilled side the skin erythema was less marked and where wet dermatitis appeared this was evident only on the side left unchilled

SUMMARY

A technique for the treatment of cancer of the larynx confined to the vocal cords using cesium unit is described The standard collimator of the apparatus was furnished with special collimator and wedges The dose distribution was determined in a tissue equivale phantom Cooling of the irradiation area of the skin in connection with the treatment seems reduce the skin reaction

ZUSAMMENFASSUNG

Eine Technik zur Behandlung der Stimmbander beim Kehlkopfkrebs mittels Caesiur Bestrahlung wird angegeben Ein Spezialkollimator und Keilfilter wurden angewend und die Dosisverteilung wurde mit einem Gewebs equivalenten Phantom ermittelt A kühlung der Haut im Strahlengebiet reduziert wahrscheinlich die Strahlenreaktion

RÉSUMÉ

Description d une technique de traitement du cancer du larynx limité aux cordes vocal au moyen d un appareil au caesium Le collimateur standard de l appareil est équipé d u collimateur spécial et de coins La distribution de dose a été déterminée dans un fantom équivalent au tissu Le refroidissement de la peau de la surface irradiée au cours du traitemer semble diminuer la réaction cutanée

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FROM RADIUMHEMMET, KAROLINSKA SJUKHUSET, AND KING GUSTAF V RESEARCH INSTITUTE, STOCKHOLM, SWEDEN

CATABOLISM OF ALBUMIN AND GAMMA GLOBULIN AFTER TREATMENT WITH IONISING RADIATION TO THE ABDOMEN

by

G. BIRKE, F. JACOBSSON, S. O. LILJEDAHL, L. O. PLANTIN and J. WETTERFORS

A series of studies has indicated that the gastrointestinal tract, the immunologic and haematopoietic systems and the gonads are the parts most sensitive to ionising radiation. As albumin catabolism normally occurs mainly in the gastrointestinal tract (BIRKE et coll. 1959, WETTERFORS et coll. 1965) it may readily be assumed that intestinal tract damage induced by ionising radiation may secondarily give rise to hypoalbuminaemia. The problem has been studied by experiments in animals (BIRKE et coll. 1962, WETTERFORS et coll. 1965). These revealed that whole body irradiation produced a considerable leakage of albumin into the damaged intestine and that accumulation of protein and its metabolites at this site was the cause of the hypoalbuminaemia observed.

During the treatment of malignant conditions with ionising radiation to the abdomen the development of hypoproteinaemia hypoalbuminaemia is not unusual in spite of strict precautionary measures. From the studies referred to above we deducted that there would be good reasons for investigating the catabolism of albumin and gamma globulin in a series of patients with carci-

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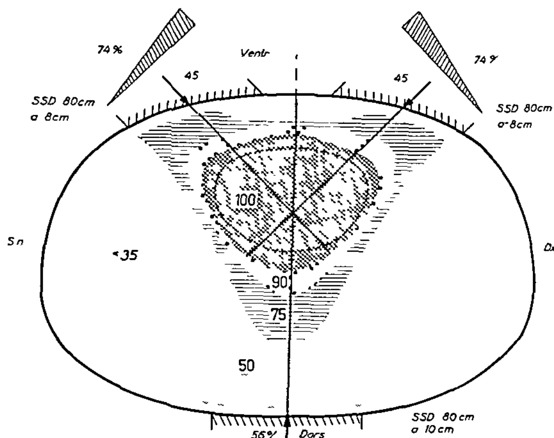


Fig 1 Dose distribution in the treatment of urinary bladder carcinoma with ^{60}Co radiation Two anterior fields with and one posterior field without wedge filter

noma of the urinary bladder and hypernephroma who were undergoing treatment with ionising radiation

Materials and Methods The investigation covered 8 cases of carcinoma of the urinary bladder in stages III—IV and ages between 52 and 71 years (six men and two women), and 3 cases of hypernephroma in ages between 59 and 72 years (two men and one woman) All the cases were treated with cobalt 60 irradiation, by means of a kilocurie cobalt machine Details of the treatment are given in Figs 1 and 2, and in Table 1

In all cases of vesical carcinoma the tumours were in an advanced stage Most of them were classified as stage T III, according to the international nomenclature The treatment technique was the same in all these cases The bladder was irradiated with a three field technique, two anterior and one posterior field (see Fig 1) the field size was of the order of 8 cm × 10 cm and

Table 1

Data on the radiologic treatment of the cases investigated

Case	Diagnosis	Tumour dose R	Treatment time days	Complications
1	Cancer of the urinary bladder	6 700	57	None
2		6 500	50	None
3		6 400	36	None
4		6 200	48	None
5		6 300	37	None
6		6 600	47	None
7		6 600	44	None
8		6 600	41	Troublesome diarrhoea
9	Hypernephroma (postoperative treatment)	6 000	42	Fatigue nausea vomiting
10		3 600	24	None
11		5 000	48	None

10 cm × 10 cm The lower field border was fixed at the inferior margin of the symphysis pubis The treatment was given daily for five days a week The total treatment period varied from 36 to 57 days and the total tumour dose from 6 000 R to 6 700 R (Table 1) The dose by volume was estimated to about 0 8 litre within the area that received a mean dose of about 6 000 R

In the planning of the treatment much consideration was given to the state of those parts of the intestine that would inevitably receive full tumour doses as established by roentgen examination of the bowel The presence of diverticulas and adhesions between the small bowel and the bladder prompted great caution in view of the risk of complications

Each case was carefully followed during the treatment period All were given sulpha drugs and Furadantin® for prophylactic purposes since one of the fundamental conditions for treatment without complications is a non infected bladder The patients had slight diarrhoea during the course of treatment only one patient suffered severe discomfort but on no occasion in all the eleven cases did it become so severe that the treatment had to be interrupted perhaps partly due to rectal injections of cortisone once a week No symptoms of small bowel complications appeared in any of the cases nor any troublesome nausea

The three cases of hypernephroma were treated postoperatively after extirpation of the diseased kidney Any residual growth present and the adjacent lymph nodes at the aorta were irradiated Great care was taken in planning of the treatment area the first consideration being to protect to the greatest extent possible the remaining kidney and the spinal cord The irradiated

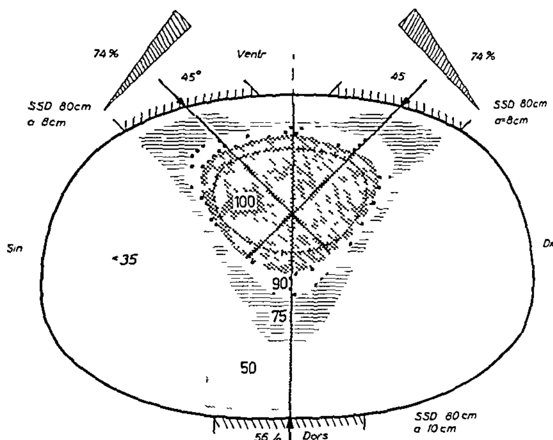


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period In seven cases the gamma globulin catabolism was also studied with ^{131}I gamma globulin Normal values and methods have been reported elsewhere (BIRKE et coll 1963)

Results

Data relating to the intravascular albumin pools and relative as well as absolute albumin degradation before and after radiation therapy, are collected in Table 2 in which the values representing faecal losses of activity, corresponding to leakage of ^{131}I albumin into the distal part of the intestinal tract are also indicated These losses are not included in the record of the metabolic figures

It may be seen from Table 2 that albumin catabolism expressed in percentage and gram per 24 hours as well as the intravascular albumin pool were normal in most cases before beginning the treatment

A moderate decrease of the intravascular albumin pool occurred in several cases after radiation therapy but the mean decrease for the whole material was not significant The relative degradation was markedly increased in two of the vesical carcinoma patients (Cases 1 and 4) but remained fairly unchanged in the others, it was even lower following radiotherapy in Case 8 There was no decrease of the albumin pool in the three hypernephroma cases, these patients received blood transfusions during the treatment however In Cases 9 and 11 the relative degradation was clearly raised

In comparison with the pretherapeutic values the faecal losses of activity were distinctly increased in all except Cases 1 and 6 Excessive values were only reached in four cases, however The losses did not exceed 1 % of the given dose in any of the hypernephroma cases (compare Table 2)

The catabolism of gamma globulin after the treatment was compared in seven of the cases with the results from 15 normal cases used in another investigation (BIRKE et coll 1963) (Table 3) The catabolic rate was significantly higher in the former as compared to the latter expressed in gram per day ($P < 0.01$) whereas the fractional catabolic rate was not significantly different As in the albumin studies the gastro-intestinal losses are not included in the results for the catabolism of gamma globulin The intravascular gamma globulin pool was significantly increased ($P < 0.05$) The mean faecal activity also studied for an average of 7 days was 0.9 % of the given dose which implies values three times as high as normal ($P < 0.01$)

The investigation has thus shown that treatment with ionising radiation to the abdomen with strict precautionary measures to protect the gastro intestinal tract from damage had a moderate effect on the intravascular albumin as

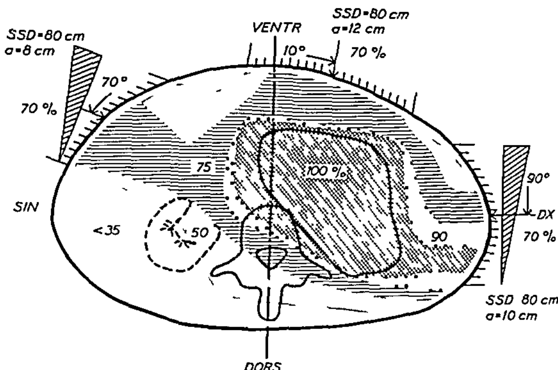


Fig. 2. Dose distribution in the treatment of hypernephroma with ^{60}Co radiation. One anterior field without and two lateral fields with wedge filter.

volume was throughout fairly great, however, and as always happens the general reactions resulting from this treatment were more marked than those that follow therapy for cancer of the bladder. The field size was about 10 cm × 20 cm, one anterior and two lateral fields were used (see Fig. 2). The total tumour dose varied between 3 600 R and 6 000 R, and the total period of treatment was 24 to 48 days. Marked general effects including considerable *fatigue and nausea, were recorded in Case 9, which received the highest* dose (6 000 R over 42 days). Recovery was not fully complete until about two months after completion of the treatment.

Metabolic studies. The total protein in the serum was determined by Kjeldahl's technique and the albumin and globulin by paper electrophoresis. The technique used in the metabolic studies with ^{131}I albumin have been described in detail elsewhere (WETTERFORS et coll. 1963, 1965, WETTERFORS 1965). The fractional catabolic rate was calculated by the method of CAMPBELL et coll. (1956), i.e. from the excreted activity in relation to the amount of circulating activity. Metabolic studies of albumin breakdown were made before the irradiation treatment, and subsequently during the last 14 days of the treatment

Table 3

Gamma globulin degradation and faecal losses of radioactivity after irradiation — The differences between these figures and those of the controls are significant

Case	Intravascular gamma globulin pool	Gamma globulin degradation (per day)		Loss of ^{131}I gamma globulin in faeces in % of dose
		Relative values	Absolute values	
		In % of intravascular pool	In gram	
2	63	8.5	5.4	1.40
3	38	7.9	3.0	—
7	—	4.?	—	1.24
8	32	5.2	1.6	0.65
9	41	10.9	4.5	1.15
10	46	6.1	2.8	0.52
11	93	5.9	5.5	0.44
Mean ± SD	52.1 ± 22.6	7.0 ± 2.3	3.8 ± 1.6	0.91 ± 0.43
Control	37.6 ± 19.8	4.8 ± 0.7	1.8 ± 0.4	0.25 ± 0.18
	P ~ 0.05	P < 0.05	P < 0.01	P < 0.01

could be established between post irradiation hypoalbuminaemia and gastro intestinal damage

PALMER & SULLIVAN (1959) observed that the same degree of hypoalbuminaemia was induced at whole body irradiation as at irradiation of the gastro intestinal tract and they suggested that this probably could be explained either by a direct effect on the intestinal tract or by an indirect effect on the liver with inhibition of the albumin synthesis BARANDUN et coll (1960) and SULLIVAN (1960) noted an increased intestinal loss of ^{131}I PVP with a maximum on the 4th post irradiation day

Experiments in animals have disclosed that a markedly increased leakage of albumin into the intestine with accumulation in the gastro intestinal tract occurs together with hypoalbuminaemia and raised albumin catabolism (BIRKE et coll 1962 WETTERFORS et coll 1965) The increase in gastro intestinal leakage therefore seems to be the explanation of the occurrence of hypoalbuminaemia after whole body irradiation

Not seldom however hypoalbuminaemia is noted also after ionising radiation for therapeutic purposes ACKERMAN et coll (1960) observed a higher degree of hypoalbuminaemia after abdominal field than after breast field irradiation On the other hand the relative gamma globulin concentration

Table 2

Relative and absolute albumin degradation and faecal losses before and after irradiation — The increase in faecal radioactivity after irradiation is significant otherwise no noteworthy differences

Case	Intravascular albumin pool before and after treatment		Albumin degradation (per day) before and after irradiation				Loss of ^{131}I albumin in faeces (% of dose) before and after irradiation	
			Relative values in % of intravascular pool		Absolute values in g and g/kg			
	Before	After	Before	After	Before	After	Before	After
1	131	110	7 9	11 6	10 4/0 19	12 8/0 23	0 28	0 21
2	196	188	10 1	7 4	19 8/0 21	13 9/0 16	0 27	0 38
3	185	166	10 9	9 8	20 2/0 25	16 3/0 20	0 49	7 47
4	187	141	9 6	13 3	18 0/0 24	18 8/0 25	0 35	9 77
5	184	182	7 7	8 5	14 2/0 21	15 5/0 23	0 13	0 47
6	176	147	9 9	9 2	17 4/0 23	13 5/0 18	0 24	0 23
7	118	118	11 0	8 0	13 0/0 22	9 4/0 16	0 20	3 27
8	—	161	14 4	7 6	—/—	12 3/0 19	0 50	2 35
9	114	144	13 4	19 0	15 3/0 22	27 4/0 39	0 34	0 52
10	154	159	12 7	10 4	19 6/0 29	16 6/0 24	0 06	0 40
11	132	158	3 1	7 3	4 1/0 06	11 5/0 18	0 12	0 39
Mean ± S D	158 ± 32	152 ± 24	10 1 ± 3 1	10 2 ± 3 5	15 2 ± 5 1 / 0 21 ± 0 06	15 3 ± 4 8 / 0 22 ± 0 06	0 27 ± 0 15	2 31 ± 3 31
Controls	128 ± 21		8 9 ± 1 1		0 175 ± 0 04		< 0 5	

well as on the gamma globulin There was increased gastro intestinal leakage of albumin and gamma globulin The absolute values for the catabolism of gamma globulin were increased after treatment with ionising radiation The figures were compared with those of normal cases, because, with the planning of the present investigation, the gamma globulin studies could not be made before the radiation treatment

Discussion

The fact that the gastro intestinal tract is one of the more radiosensitive organ systems, as rapid destruction of the epithelium is noticeable in the first post irradiation week, and that quantitatively this organ systems plays an important part in the catabolism of serum albumin prompted the present investigation, undertaken with the aim of finding out whether a relationship

ZUSAMMENFASSUNG

Der Verlust von Albumin und Gamma Globulin durch den Darm nach Strahlenbehandlung des Abdomens wurde mittels isotopgemerktem Protein in acht Fallen von Blasenkrebs und drei Fallen von Hypernephrom untersucht Auch wenn die Bestrahlung gut abgegrenzt ist tritt Proteinverlust auf bei geeigneten vorbeugenden Massnahmen konnten keine schadliche Storungen der Albumin oder Gamma Globulin Konzentration festgestellt werden

RÉSUMÉ

La perte entérique d albumine et de gamma globuline due à l irradiation de l abdomen dans 8 cas de cancer de la vessie et 3 cas d hypernéphrome a été étudiée au moyen de protéines marquées par des isotopes radioactifs On a constaté que la perte de protéines a lieu meme quand le volume irradie est bien limite mais les concentrations en albumine et en gamma globuline ne sont pas perturbées quand on prend des mesures preventives

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was increased in ten of their eleven cases The results suggest that the same mechanism may be responsible for this hypoalbuminaemia, and the present einvstigation has revealed that an increased leakage of albumin and gamma globulin can occur, in spite of careful planning to ensure the smallest possible dose to the intestinal tract, especially the small bowel Since the faecal excretion of radioactivity was distinctly increased in most of the vesical carcinoma cases but no rise in urinary activity, with one exception, was observed, it may be concluded that the intestinal leakage of protein occurred in the lower part of the small bowel or in the colon Were the damage in the upper part of the gastro intestinal tract, and the leakage occurred there, as in the hypernephroma cases, the protein would be broken down in the intestinal tract and the degradation products absorbed and excreted with the urine This would result in a raised catabolic rate

This investigation has disclosed that loss of protein may occur in spite of every precaution although in the present cases it was not very extensive or was largely compensated for by increased albumin synthesis in the liver Thus, no detrimental effects on either the albumin or the gamma globulin concentration in the blood were noted In cases in which malignant tumours necessitate treatment of larger fields, on the other hand, there are obvious risks of intestinal damage, with great losses of protein resulting in hypoproteinaemia The results obtained emphasize the risks attending treatment with ionising radiation to the abdomen and indicate that precautionary measures are necessary in order to avoid hypoproteinaemia after a treatment in which the gastro intestinal tract has been exposed

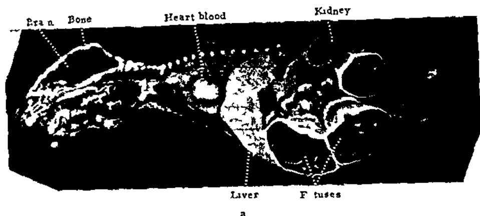
Experiment in animals, as well as the present study, suggest that the condition with increasing loss of protein is apparently transient, and the sequelae are relatively easy to overcome when therapeutic radiation doses are used Intestinal complications following megavoltage radiation to the abdomen, of the type described by EDWARDS (1965), offer quite different problems as regards over all treatment time

Acknowledgement

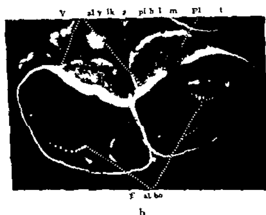
This investigation was supported by grants from the Stockholm Anti Cancer Society and the Research Delegation for Defence Medicine

SUMMARY

Investigations by means of isotope labelled proteins on the enteric loss of albumin and gamma globulin caused by ionising radiation to the abdomen in 8 cases of carcinoma of the bladder and 3 cases of hypernephroma are described It was found that losses of protein occur even when the radiation is well circumscribed but that no detrimental effects on the albumin or gamma globulin concentrations occurred when precautionary measures were taken



a



b

Fig 1 a) Autorad ogra n of a pregnant mou e 24 hours aft r intravenous j ction of zirconium 95 in quilibrium w th its daughter isotope n ob um 95 R ther h gh concentration in the bl ood and accumu l t n of r dioactivity i i maternal bone v sce al yolk sac epithel um and fetal bone b) D tail of (a) how ng two fetuses pl e tas and adjacent fetal membranes There s a h gh uptake of z conium ni bium n the fetal bone in the v ceral yolk sa ep thel um

of the body The physical half life of ^{95}Zr is 65 days and it decays into ^{95}Nb which has a half life of 35 days At the time of injection ^{95}Zr was in equilib brium with ^{95}Nb and the autoradiograms will therefore also show the distri bution of ^{95}Nb In addition a series of autoradiograms were prepared after injection of pure ^{95}Nb

Methods Zirconium 95 in equilibrium with niobium 95 and pure niobium 95 were obtained from the Radiochemical Centre Amersham England The isotopes were obtained as oxalate complexes in 0 5 % oxalic acid which was then diluted with physiologic saline Each mouse was injected in a tail vein with 0 2 ml corresponding to 25 μCi

Twelve adult male mice weighing about 20 g and 6 female mice in advanced

FROM THE DIVISION OF RADIOBIOLOGY, RESEARCH INSTITUTE OF NATIONAL DEFENCE, SUNDBYBERG, AND THE DEPARTMENT OF PHARMACOLOGY, ROYAL VETERINARY COLLEGE, STOCKHOLM, SWEDEN

DISTRIBUTION OF ZIRCONIUM AND NIOBIUM IN MICE

Autoradiographic study

by

JORGEN BACKSTROM, LARS HAMMARSTROM and ARNE NELSON

Zirconium 95 and niobium 95 constitute during the first year about 20 per cent of the total activity of fission products aged from a few days to one year (RADIOLOGIC HEALTH HANDBOOK 1960). The isotopes have been identified in food (FUJITA et coll. 1963) and in the human body (RUNDO & NEWTON 1962, 1965, and MACDONALD et coll. 1963). When orally administered, ^{95}Zr and ^{95}Nb are absorbed to a rather small extent (HAMILTON 1947, THOMAS et coll. 1961, VAN DILLA 1960, EKMAN & ÅBERG 1961), but when inhaled the absorption through the lungs is considerable (SCHIESSLE et coll. 1961). This suggests the need for further information on the distribution in the body of the two compounds. Measurements of the radioactivity by impulse counting have been used in earlier investigations of the distribution of ^{95}Zr and ^{95}Nb in organs and tissues (MATTHEWS & GARTSIDE 1965).

In the present investigation whole body autoradiography has been used in order to get more information on the distribution in tissues, organs and fluids

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Both isotopes seemed to pass the placenta and were accumulated in the fetal bone liver and blood The placental transfer has also been studied in rabbits and a similar localization was found in the fetuses of rats (MACDONALD et coll 1965)

A marked concentration was observed in the visceral yolk sac epithelium Some other elements have also shown an accumulation in this site when injected intravenously e g vanadium 48 (SORENMARK & ULLBERG 1961) yttrium (APPELGREN et coll 1966) mercury 203 (BERLIN & ULLBERG 1963) and plutonium 239 (ULLBERG et coll 1962) The chemical properties of these compounds as well as their distribution patterns in the body, differ in many respects and the mechanism responsible for the accumulation and retention in the visceral yolk sac epithelium of these elements requires further investigation

Ruthenium 103 like ^{95}Nb and ^{95}Zr ^{95}Nb showed affinity for connective tissue and the distribution patterns after injection were quite similar Ruthenium however did not accumulate as strongly in bone as the other isotopes

Acknowledgement

The authors acknowledge the valuable advice and criticism received from Associate Professor Sven Ullberg

SUMMARY

Zirconium 95 in equilibrium with niobium 95 and pure niobium 95 were intravenously injected into mice and the distribution of the isotopes after different time intervals was studied by whole body autoradiography The distribution patterns were quite similar The radioactivity persisted for a long time in blood and finally accumulated in bone and connective tissue

ZUSAMMENFASSUNG

Zirkonium 95 in Äquilibrium mit Niobium 95 und reinem Niobium 95 wurden in Mäusen intravenös injiziert Bei Untersuchungen mittels Ganzkörper Autoradiographie wurde eine ähnliche Distribution der Isotopen nach verschiedenen Zeitintervallen nachgewiesen Die Radioaktivität verblieb während langer Zeit in dem Blut und akkumulierte schliesslich in den Knochen und dem Bindegewebe

RÉSUMÉ

Les auteurs ont injecté à des souris par voie intraveineuse du zirconium 95 en équilibre avec du niobium 95 et du niobium 95 pur Ils ont étudié à différents intervalles de temps par autoradiographie de tout le corps la distribution de ces isotopes Les types de distribution sont très semblables La radioactivité reste longtemps dans le sang et s accumule finalement dans l os et le tissu conjonctif

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Autoradiographic study

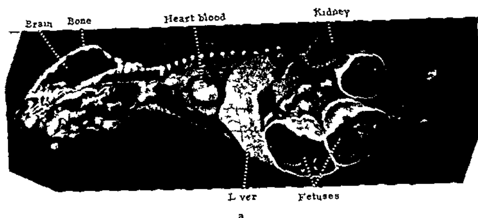
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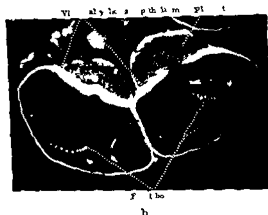
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In the present investigation, whole body autoradiography has been used in order to get more information on the distribution in tissues, organs and fluids

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a



b

Fig 1 a) Autoradiogram of a pregnant mouse 4 hours after intravenous injection of zirconium 95 in equilibrium with its daughter isotope niobium 95 Rather high concentration in the blood and accumulation of radioactivity in maternal bone visceral yolk sac epithelium and fetal bone b) Detail of (a) showing two fetuses placenta and adjacent fetal membranes There is a high uptake of zirconium niobium in the fetal bone in the visceral yolk sac epithelium

of the body The physical half life of ^{95}Zr is 65 days and it decays into ^{95}Nb which has a half life of 35 days At the time of injection ^{95}Zr was in equilibrium with ^{95}Nb and the autoradiograms will therefore also show the distribution of ^{95}Nb In addition a series of autoradiograms were prepared after injection of pure ^{95}Nb

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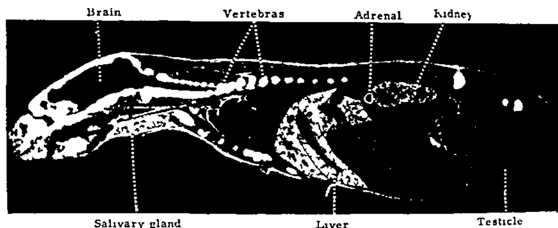


Fig 2 Autoradiogram of a male mouse 4 days after intravenous injection of zirconium 95 in equilibrium with the daughter isotope niobium 95 The isotope concentration is highest in the skeleton it is also rather high in the liver salivary glands and kidney The isotope is also localized to the connective tissue especially the capsule around adrenal and subcutis

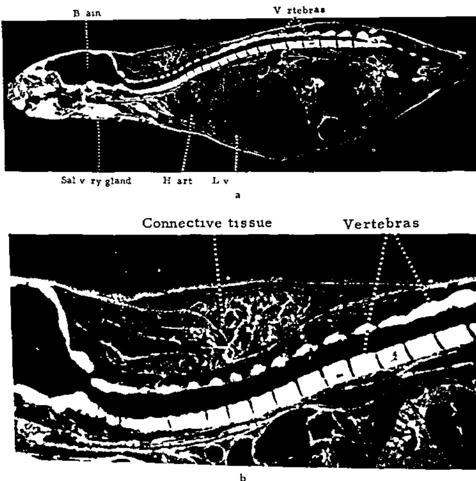
pregnancy weighing about 40 g, were used as experimental animals Six male mice and 3 female mice were injected with ^{95}Zr-^{95}Nb, and another similar series was injected with niobium 95 The intervals between injection and sacrifice were for the male mice 5 min, 20 min, 1 hour, 4 hours, 24 hours, and 4 days, and for the female mice 20 min, 4 hours and 24 hours

The animals were sacrificed by immersion in hexane, cooled to — 75° C with solid CO_2 Sagittal, 20 micron thick, sections through the whole animals were cut at — 10° C The sections were dried at the same temperature, and autoradiographic exposure was made by apposition against Structurix X ray film (Gevaert) The exposure time was 4 to 12 days The autoradiographic method has previously been described in detail (ULLBERG 1954, 1958)

Results

The autoradiographic distribution patterns after injection of ^{95}Zr ^{95}Nb, or ^{95}Nb did not show any great differences but the bone seemed to accumulate more radioactivity after injection of ^{95}Zr ^{95}Nb The results given below are therefore representative of both ^{95}Zr-^{95}Nb and ^{95}Nb

The concentration in the blood was high initially and decreased very slowly The uptake in the tissues was also rather slow and the radioisotopes gradually accumulated in connective tissue and bone In the pregnant mice, a slow increase to a final high concentration was also observed in the visceral yolk sac epithelium The distribution in various tissues at different time intervals ...cribed in detail below



F g 3 a Auto d ogram of a mal mouse 4 days after ntravenous nject on of niob um 95 The gr test a umulat on of the isotope is n the s leton l v and salivary glands also rathe h gh ad o t ty n th conn tiv tis ue b) Deta l of (a) show ng a high uptake of n obium 95 in the b ne a d in the onnect e t u of the neck region

In the *circulatory system* the blood retained a high concentration of the radioisotopes for more than 24 hours After 4 days the concentration had decreased to a low level in the blood but in the connective tissue in the walls of the blood vessels and in the myocardium the radioactivity remained

No radioactivity was observed in the *nervous tissues* with the exception of the choroid plexus which showed a long lasting uptake

In the *digestive system* the concentration of the radioisotopes was rather low

at all intervals studied No gastric excretion was observed In the intestinal contents, *a moderate concentration of radioactivity* was observed at 4 and 24 hours The uptake in the liver, pancreas and salivary glands seemed to correspond to the concentration in the blood during the first day, but at 4 days the radioactivity in these organs exceeded that of the blood No activity was found in the gallbladder or in the biliary ducts

The concentration in the *respiratory system* reflected that of the blood

The *urinary system* had a high concentration and seemed to constitute the main excretion route The contents of the pelvis of the kidney as well as of the urinary bladder were strongly radioactive during the first four hours after injection A moderate accumulation was observed in the kidney also after longer times

The concentration in the *endocrine system* during the first day seemed to reflect *the concentration in the blood but also later some radioactivity persisted in the* interstitial tissues and surrounding connective tissue

In the *bone*, the isotopes accumulated strongly for a long time The uptake seemed to be higher after injection of ^{95}Zr-^{95}Nb than after ^{95}Nb alone Uptake was also observed in the permanently growing incisors, it seemed to be highest in the dentin

Uptake was observed in the *tracheal cartilage* but in no other cartilage

The *fascial membranes*, as well as other connective tissue, showed a marked concentration of the isotopes, which still existed after four days

In the *mammary glands*, a moderate concentration was noted

In the *placenta*, the initial concentration followed that of the blood, but gradually the visceral yolk sac epithelium accumulated radioactivity and at 24 hours the concentration in this organ was much higher than in the blood Both isotopes to some extent seemed to pass by the placenta The strongest uptake was noted in the fetal bone A weak uptake was also observed in the *fetal liver and blood*

Discussion

The distribution patterns after injection of ^{95}Zr-^{95}Nb and ^{95}Nb were very similar except for the stronger uptake of radioactivity in bone after *injection* of ^{95}Zr-^{95}Nb This is in agreement with the quantitative studies of Shastry et coll (1964) and MacDonald et coll (1965) The very low uptake of ^{95}Nb in bone of the adult rabbit (MacDonald et coll 1965), however, was not confirmed in the present studies According to our autoradiograms, bone also accumulated ^{95}Nb to a considerable extent

The concentration in blood remained high for a long period after injection, which probably was due to the formation of metal complexes with the plasma proteins (Mealy 1957)

Both isotopes seemed to pass the placenta and were accumulated in the fetal bone liver and blood The placental transfer has also been studied in rabbits and a similar localization was found in the fetuses of rats (MACDONALD et coll 1965)

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INFLUENCE OF GESTATION AND LACTATION ON RADIOSTRONTIUM INDUCED MALIGNANCIES IN MICE

II Retention of radiostrontium and relation between tumour incidence and excretion rate

by

A NILSSON A NELSON C RONNBACK A M SJODEN G WALINDER an
O HERTZBERG

In the first paper in this series NILSSON (1966) reported that gestation an lactation influence the induction by ^{90}Sr of malignancies in mice The late time was extended and the bone tumour rate was decreased in the mate lactating group in comparison with the unmated group This effect on th tumour induction appears to be due to decrease in the skeletal content of ^{90} caused by gestation and lactation even if additional hormonal facto cannot be excluded

The transfer of radiostrontium to the foetuses during gestation and to t young during lactation has been the subject of several investigatio (HOLMBERG et coll 1960 KRIEGEL 1960 STERNBERG 1960 NELMAN & KRI GEL 1961 KOLLMER & KRIEGEL 1963 NELSON et coll 1965)

In an attempt to obtain a more accurate quantitative relationship betwe the amount of radiostrontium in the skeleton and the induction of mal

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Table 1

Experimental schedule

Treatment groups	Number of animals measured after			
	1 week	1 month	2 months	3 months
Control (unmated)	25	25	25	25
Mated	25	25	25	25
Mated giving suck	25	25	25	25

nancies we measured the retention in the following groups of female mice at various times after administration of ^{85}Sr unmated, mated only, and mated giving suck Both the radioactivity of the whole body and of important individual bones were measured

Material and Methods In this experiment, 300 female CBA mice (approximately 70 days old) were used All the animals were injected intravenously with 0 2 to 0 3 ml of a solution of strontium 85 nitrate in physiological saline

The 300 females were divided into three groups with 100 animals in each (Table 1) One group served as a control group in which the females were unmated These were kept with five animals in each cage In the other two groups, one female and one (untreated) male were caged together throughout the experiment The matings occurred immediately after the injections In one of these two groups, the mated females gave suck to their litters during twenty days, in the other group the litters were taken away immediately after birth The number of young at birth was noted in these two groups

The animals were measured by whole body counting both immediately after injection and at the time they were sacrificed, i e after 1 week, 1 2 or 3 months At the time of sacrifice, parts of the skeleton were taken out and measured by means of a well type crystal

The whole body measurements were performed in a small animal counter (NILSSON 1961) consisting of a plastic crystal as detector attached to a photo multiplier tube connected to a conventional counter unit

The amount of radioactivity administered gave a rate of about 85 000 counts per minute at the initial measurement within three minutes following the injection The results of measurements are expressed in per cent of the initial measurement (100 %) for each animal The means and standard errors have been calculated from these values

Table 2

Measurements of activity at different times after injection (expressed in per cent of initial measurement of all numbers from groups of 25 animals)

Treatment groups	Activity (mean ± SE)			
	1 week	1 month	2 months	3 months
Control (unmated)	36.8 ± 0.89	22.0 ± 0.58	14.0 ± 0.11	8.2 ± 0.26
Mated	34.6 ± 0.94	21.3 ± 0.56	12.0 ± 0.[illegible]4	7.5 ± 0.20
Mated giving suck	3[illegible].6 ± 0.73	18.2 ± 0.39	7.9 ± 0.36	5.2 ± 0.23

Table 3

Comparison between the different groups in table 2 (t values and levels of significance)

Comparison	1 week	1 month	2 months	3 months
Control vs mated	1.71	0.87	3.64 p (t>3.51) = 0.01	2.13 p (t>2.01) = 0.05
Control vs mated giving suck	1.04	5.47 p (t>3.51) = 0.01	16.3 p (t>3.51) = 0.01	8.65 p (t>3.51) = 0.01
Mated vs mated giving suck	0.84	4.55 p (t>3.51) = 0.01	6.32 p (t>3.51) = 0.01	7.57 p (t>3.51) = 0.01

At the four time intervals mentioned above twenty five females from each of the three main groups were killed and from each animal femur tibia pelvis lumbar vertebrae sacral vertebrae humerus and skull were collected The radioactivity in these bones was then measured in a well type crystal connected to a counter unit

Results

Whole body counting Tables 2 and 3 and Fig 1 represent the results of the investigation The activity at different times after the administration of ^{85}Sr is given in Table 2 in per cent of the initial measurement in each of the three experimental groups As expected, there is no significant difference between the three groups after one week After one month there is still no difference between the unmated group and the mated not giving suck group The difference between the two mated groups is however significant After two months the difference between all the three groups are significant At three months the difference between the unmated and the mated not giving suck groups is less pronounced but the other differences are still significant

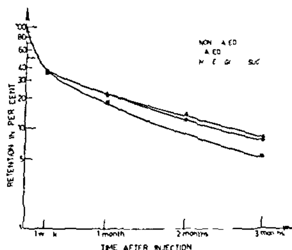


Fig 1 Whole body counting of retention of ^{85}Sr

It is apparent from the results that the enhancement of excretion of ^{85}Sr caused by lactation is greater than that caused by gestation only, with a lower retention in the females giving suck than in those not giving suck

The number of young is an important factor in the evaluation of the effect of gestation and lactation on the maternal retention of ^{85}Sr It is, however, first necessary to investigate whether or not there is a difference in the number of young in the two mated groups, i e whether giving suck influences the fertility

In Table 4, the increasing numbers of young per female at different times during the experiment are given In the suckling group, there is a slightly higher number of young at 1 and 2 months, but at 3 months the situation is reversed The difference is, however, not great enough to explain any difference in activity at the same time

In Fig 2, the relationship between retention in per cent of the initial measurements of ^{85}Sr is shown at 1, 2 and 3 months and for different numbers of young in the mated only groups and in the giving suck groups After one month the difference between the radioactivity in the three groups is insignificant, even though there is a tendency toward lower values in the giving suck

Table 4

Mean number of young per female at different times

Treatment groups	1 month	2 months	3 months
Mated	6 00	13 9[illegible]	18 0[illegible]
Mated giving suck	5 56	11 9[illegible]	23 90

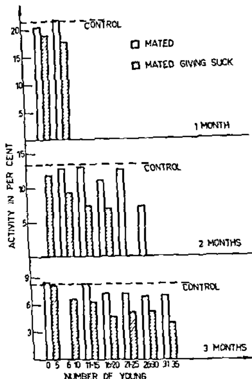


Fig 2 Relation between number of young and retention of Sr at 1 2 and 3 months after administration

group After 2 months however the retention in all the mated groups is throughout lower than in the controls less marked in the mated only but certainly apparent in the giving suck group In this latter group a levelling of the retention values is observed after 11 to 15 and 16 to 20 young in which cases the activity values are only about half of the values of the unmated groups After 3 months there is a general but slight decrease in those mated only groups which had more than 16 young The decrease is marked in the giving suck groups with more than 16 young As was the case after 2 months there seems to be approximately a 50 % decrease in comparison with the controls

Gestation as well as lactation has the ability to enhance the excretion of radiostrontium from the mother s skeleton i e decrease the retention in comparison with unmated females However the effect of gestation only is very small It is obvious on the other hand that the influence of lactation is great In both cases the decrease is dependent on the number of young and

Table 5

Results of measurements (cpm in thousands mean ± standard error n = 25)

Treatment	Femur	Tibia	Pelvis	Lumbar vertebrae	Sacral vertebrae	Humerus	Skull
1 week							
Control	3.41 ± 0.10	2.50 ± 0.07	2.94 ± 0.08	7.02 ± 0.21	3.70 ± 0.14	1.77 ± 0.05	22.05 ± 0.58
Mated	3.03 ± 0.09	2.19 ± 0.07	2.73 ± 0.08	6.97 ± 0.23	2.95 ± 0.13	1.56 ± 0.04	20.59 ± 0.50
Mated giving suck	3.14 ± 0.08	2.43 ± 0.06	2.92 ± 0.06	7.26 ± 0.20	3.51 ± 0.14	1.81 ± 0.08	21.47 ± 0.45
1 month							
Control	2.31 ± 0.06	1.71 ± 0.04	1.91 ± 0.05	4.32 ± 0.13	2.19 ± 0.09	1.31 ± 0.03	14.83 ± 0.47
Mated	2.09 ± 0.05	1.49 ± 0.03	1.59 ± 0.03	3.46 ± 0.09	1.83 ± 0.06	1.14 ± 0.03	14.86 ± 0.13
Mated giving suck	2.05 ± 0.05	1.60 ± 0.02	1.62 ± 0.03	3.03 ± 0.21	1.78 ± 0.06	1.27 ± 0.03	14.80 ± 0.07
2 months							
Control	1.45 ± 0.01	1.03 ± 0.02	1.12 ± 0.02	2.24 ± 0.07	1.37 ± 0.05	0.82 ± 0.02	8.11 ± 0.16
Mated	1.28 ± 0.04	0.96 ± 0.04	0.92 ± 0.02	1.56 ± 0.06	0.99 ± 0.04	0.73 ± 0.07	7.64 ± 0.19
Mated giving suck	1.01 ± 0.03	0.82 ± 0.02	0.75 ± 0.03	0.95 ± 0.07	0.66 ± 0.03	0.68 ± 0.02	6.97 ± 0.17
3 months							
Control	0.97 ± 0.02	0.70 ± 0.02	0.73 ± 0.02	1.48 ± 0.05	0.84 ± 0.04	0.57 ± 0.01	4.76 ± 0.12
Mated	0.90 ± 0.07	0.66 ± 0.06	0.64 ± 0.06	0.92 ± 0.08	0.60 ± 0.06	0.51 ± 0.05	5.01 ± 0.26
Mated giving suck	0.84 ± 0.03	0.55 ± 0.02	0.49 ± 0.02	0.56 ± 0.04	0.43 ± 0.02	0.46 ± 0.01	4.39 ± 0.11

occurs approximately during the first two months after administration of radiostrontium. Later decrease is insignificant.

Radioactivity measurements in individual bones. The results of the measurements of the activity of individual bones are shown in Table 5 where each point represents data from bones of 25 animals. The activity in the bones is given in counts per minute, and no reference has been made to initial measurements as was the case with the whole body counting where the animals constituted their own references.

A slight difference between the activity levels of the different groups is observed on the 7th day, at which time the activity of the control group in most cases exceeds that of the mated groups. This is probably due to a difference in the amount of radiostrontium injected since the first week of gestation could not have any effect on the excretion rate of strontium.

Table 6

Slopes of regression lines (decrease in $\log_e$ cpm per week × 100)

	Control b_c	Mated b_m	Mated giving suck b_{ms}
Femur	5 28	5 33	7 15
Tibia	5 48	5 14	6 72
Pelvis	5 95	6 68	8 44
Lumbar vertebrae	7 10	9 34	12 89
Sacral vertebrae	6 09	6 74	10 39
Humerus	4 77	4 73	6 13
Skull	6 23	6 11	7 09

When calculating the mean and standard error from the measurement value (x) the ratio standard error/mean was found to be fairly constant for every kind of bone during the first two months.

The values x were therefore transformed according to $y = \log x$ in which case the standard errors of the y values became satisfactorily constant with time for each kind of bone.

This transformation also leads to a linear relation between y and time after injection for the first three times of measurements namely 1 week, 1 and 2 months.

Regression analysis has then been made based on these three occasions. For each treatment and kind of bone a straight line was fitted by means of the least square method. If this line is extended the 3 month values are in all cases situated above the line. Table 6 shows the slopes of the calculated regression lines.

For each bone the slopes were compared between the three groups. The ratio between the difference of the regression coefficients and the standard error for that difference has been calculated (Table 7). These ratios can be tested by means of the t distribution.

It appears from Tables 6 and 7 that the differences between the excretion rates of the different bones in the control group and in the mated group are not significant except in the pelvis and the lumbar region. When the control group is compared with the mated group giving suck the differences are significant in all bones. The smallest difference is observed for the skull. The comparison between the mated group and the mated group giving suck gives similar results. It is however, apparent that the differences are mainly due to the high values of the regression coefficients in the mated giving suck group i e the high excretion rates in this group.

Table 7

t values for difference between the slopes in table 6

	Control vs mated	Control vs mated giving suck	Mated vs mated giving suck
Femur	< 1.98	5.25	5.17
Tibia	< 1.98	4.32	5.00
Pelvis	2.38 $p < 0.05$	8.47	5.64
Lumbar vertebrae	5.23 $p < 0.001$	12.56	7.29
Sacral vertebrae	< 1.98	7.36	7.85
Humerus	< 1.98	4.28	4.32
		(Femur–Humerus: $p < 0.001$)	(Femur–Humerus: $p < 0.001$)
Skull	< 1.98	2.83 $p < 0.01$	3.14 $p < 0.01$

As in the case of whole body counting the enhanced rate of excretion of ^{85}Sr is mainly due to lactation. The gestation influences the pelvic and lumbar regions only. The effect of gestation and lactation is great for two months after administration of radiostrontium. Later on the influence on the excretion rate is much lower.

Relation between tumour incidence and excretion rate

From the first of these papers, in which NILSSON reported on his investigation on the incidence, distribution and characteristics of ^{90}Sr induced malignancies, it is apparent that gestation and lactation had a diminishing effect on the tumour rate. The rate for the mated group giving suck was about 50 % of that for the unmated group. It should be noted that the results of the whole body counting showed that the retention of ^{85}Sr at 2 months after administration in the mated giving suck group had decreased to about 50 % of the retention of the unmated group and of the mated not giving suck group.

The localization and characteristics of the tumours are also influenced. The decrease in tumour rate varies in the different bones. As an expression of this decrease we have used the relative difference (RD) for each bone according to the following formula

$$RD = \frac{T_x - T_{m}}{T_x}$$

where T_c is the number of tumours in the controls, i.e. unmated group, T_{ml} the number of tumours in the mated giving suck group, and x the bone in question.

Table 8

Relative differences between number of tumours in mated and unmated groups

Site of tumours	Number of tumours		$\frac{T_c - T_m}{T}$
	Unmated (T)	Mated giving suck (T_{ms})	
Femur	205	139	0 32
Tibia	95	58	0 39
Humerus	101	76	0 25
Femur + tibia	4	7	−0 75
Total long bones	405	280	0 31
Pelvic bone	79	25	0 68
Cervical spine	7	9	−0 29
Thoracic spine	10	7	0 30
Lumbar spine	56	4	0 93
Sacral spine	48	3	0 94
Sacral + lumbar spine	8	1	0 88
Coccygeal spine	5	1	0 80
Total vertebral column	134	25	0 81

The calculated relative differences are shown in Table 8 from which can be seen that the RD s are different in the various bones The RD is low in the long bones and negative for tumours involving both femur and tibia The number of tumours is however very low and does not significantly influence the RD of the total of the long bones In the lower part of the spine including the lumbar sacral and coccygeal vertebrae the RD s are very high The RD s for the thoracic vertebrae are low and for the cervical part negative In this case also the number of tumours is very low The RD of the whole vertebral column is however high The RD of the pelvis is intermediate

In an attempt to find a relation between the decrease in the tumour rate and the enhanced excretion rate the relative differences of the slopes of the regression lines from Table 6 were calculated (see Table 9) in a similar way

The relative differences of the tumour incidence have been compared with the relative differences of the slopes (Table 10) It is apparent from the table that there is a very good agreement between the decrease in tumour rate and the enhanced excretion rate caused by gestation and lactation It is also possible to distinguish three different groups one group consisting of lumbar and sacral vertebrae with high relative differences a second group

Table 9

Relative differences between slopes of regression lines

Bone	Slope of		$\frac{b_{ms}-b_c}{b_c}$
	Unmated (b_c)	Mated giving suck (b_{ms})	
Femur	5.28	7.15	0.35
Tibia	5.48	6.72	0.23
Pelvic bone	5.95	8.44	0.42
Lumbar spine	7.10	12.89	0.82
Sacral spine	6.09	10.39	0.71
Humerus	4.77	6.13	0.29
Skull	6.23	7.09	0.14

consisting of femur, tibia and humerus with low relative differences and a third group, pelvis only, with an intermediate value.

The investigation of the incidence, distribution and characteristics of the ^{90}Sr induced tumours has shown that the tumour incidence in mated mice giving suck is only about half of that in the unmated animals. The decrease of the tumour rate in the individual bones is greatest in the lumbar and sacral spines and lowest in the long bones.

The whole body counting of ^{85}Sr retention, and the measurement of the activity in certain individual bones, have shown that lactation, within two months after administration of ^{85}Sr, decreases the activity in the mated mice giving suck to about half of the activity in the unmated mice.

The degree of decrease in tumour incidence in the individual bones appears to be related to the excretion rate of radiostrontium in the bone in question.

Discussion

Except for the present work (NILSSON 1967 and present paper) there are only two other publications which have reported a decrease in the production of ^{90}Sr induced tumours as a consequence of increased radiostrontium excretion. VAN PUTTEN (1962) has shown a beneficial effect on tumour induction with a low phosphorus diet in mice, and ZANDER PRINCIPATI & KUZMA (1964) have been able to demonstrate a similar effect after treating mice with zirconium citrate. It would be of great interest to compare the results of these two investigations with our results.

Different mouse strains and radiostrontium doses were used in the three investigations. The CBA strain was used in our experiments. VAN PUTTEN

Table 10

Relative differences of tumour incidence compared with relative differences of slopes

Bone	$\frac{T - T_{ms}}{T}$	$\frac{b_m - b_c}{b}$
Femur	0 32	0 35
Tibia	0 39	0 23
Humerus	0 25	0 29
Lumbar spine	0 93	0 82
Sacral spine	0 94	0 71
Pelvic bone	0 68	0 42

used C57 BL/Rij and ZANDER PRINCIPATI used CF1 The ^{90}Sr doses were 0 7 μCi/g 1 μCi/g and 0 20 to 0 44 μCi/g respectively The existence of tumours were in all cases established by radiographic examinations or by macroscopic appearance Furthermore NILSSON (1967) carried out microscopic investigations on the larger bones of each mouse

VAN PUTTEN found that bone tumours were the cause of death in the majority of the mice In NILSSON s study 98 % in the unmated group and 89 % in the mated group giving suck died with bone tumours Only 21 7 % of the untreated group died with bone tumours in the investigation by ZANDER PRINCIPATI & KUZMA which may be attributed to the low ^{90}Sr dose The zirconium citrate treatment decreased the number of animals showing tumours to 8 0 %

In all the investigations cited the tumour rate per mouse was lower in the treated animals VAN PUTTEN observed that the incidence of tumours per mouse in the group on phosphorus deficient diet was 2 as compared with approximately 3 5 in the control diet group NILSSON observed a tumour rate of 6 5 in the unmated group and 3 6 in the mated group giving suck If only the macroscopic tumours were taken into consideration the corresponding figures were 2 2 and 1 3 It is interesting to note the good agreement between the ratios (1 7 to 1 8) in the two investigations especially since the dose reduction in both cases has been calculated to 20 to 30 %

In NILSSON s (1967) investigation the mean time interval between the ^{90}Sr injection and sacrifice was 399 ± 11 days for the mated and 212 ± 4 days for the unmated group The first tumours in the unmated group were observed 120 days after the ^{90}Sr injection

In the investigation by ZANDER PRINCIPATI & KUZMA the earliest tumour appeared after 147 days The mean time of appearance was approximately the same in the treated and untreated series with 0 44 μCi/g dose namely 296 and 291 days respectively However the mean time in mice treated with

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consisting of femur, tibia and humerus with low relative differences and a third group, pelvis only, with an intermediate value

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Except for the present work (NILSSON 1967, and present paper) there are only two other publications which have reported a decrease in the production of ^{90}Sr induced tumours as a consequence of increased radiostrontium excretion VAN PUTTEN (1962) has shown a beneficial effect on tumour induction with a low phosphorus diet in mice, and ZANDER PRINCIPATI & KUZMA (1964) have been able to demonstrate a similar effect after treating mice with zirconium citrate It would be of great interest to compare the results of these two investigations with our results

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zirconium citrate in the *0.34 μCi/g* group was 51 days longer than the comparable untreated group (329 days versus 278 days). The latency time was recorded at the time of appearance and not at time of death, however.

The anatomical distribution of bone tumours, in the investigation of ZANDER-PRINCIPATI & KUZMA, was similar in all groups. The principal sites were femurs (34.6 %), tibia (27.1 %), spine (22.1 %) and pelvis (9.1 %). These authors stated that previous experiments by VAE et coll. (1961) and SYBERS et coll. (1962) had shown that the distribution of bone tumours cannot be explained on the basis of dissimilar distribution of radiostrontium.

VAN PUTTEN, on the other hand, observed a shift in the localization of the bone tumours. In the phosphorus deficient group, only 14 % of the tumours were found in the vertebral column as compared to 40 % in the control group. In the femur, the corresponding figures were 48 % and 25 %, respectively. From his data it is evident, however, that the reduction in radiostrontium content of the bone due to the phosphorus deficient diet is very similar in the different bones of the skeleton.

NILSSON demonstrated that the distribution of ^{90}Sr tumours in the mated group giving suck was different from that in the unmated group, as 21.7 % of the tumours in the latter group were localized in the sacral and lumbar vertebrae against only 7.1 % in the mated group giving suck. The corresponding figures for the femur were 31.5 % and 42.1 %, respectively.

It is also apparent from the present investigation (Table 10) that a relationship seems to exist between the tumour rate and the excretion rate in the individual bone.

In order to facilitate further discussion, in particular with respect to which parameters of radiation dosage influence the production of ^{90}Sr induced bone tumours, the mean skeletal doses from ^{90}Sr in our tumour studies have been *estimated. The calculations were based on our measurements of* ^{85}Sr retention in the whole skeleton of the mice (Table 2) and on a regression analysis of these values.

The measurement values in Table 2 agree well with our earlier unpublished results from investigations of the retention of ^{85}Sr in CBA mice. After a great excretion rate during the first days after administration, a stabilizing of the retention appears to occur from approximately the 8th day. Thereafter the total activity of the body seems to decrease exponentially during the following half year. Our measurements have not extended beyond this time.

The regression analysis of the retention curves of the values from Table 2 shows no significant difference between the slopes of the regression lines (in a line log diagram) for the unmated and the mated only groups. On the other hand, the retention in the mated group giving suck decreases significantly

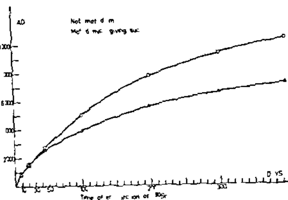


Fig 3 Calculated mean accumulated radiation dose to the mouse skeleton

from the start of lactation on the 21st day after administration This rapid excretion is however interrupted at about the 45th day from which time onward the retention curve adopts the same slope as the curves of the other two groups

The average weight of the mice at the time of administration of radiostrontium was approximately 25 g and from that the average skeletal weight was estimated to be 2 g The mean injected dose for each animal was 18 μCi per mouse (0 7 μCi/g) According to the investigations of PARMLEY et coll (1962) the absorbed energy in the whole mouse skeleton is 32 % The mean energy of ^{90}Sr ^{90}Y is 1 13 MeV per disintegration

On the basis of these data and the retention curves and assuming that no significant change in the excretion rate occurs during the remaining investigation period (from day 200 to day 400) a mean radiation dose to the mouse skeleton can be calculated (Fig 3) Obviously such a dose estimate does not give any relevant idea of the dose to the population of bone cells in which the tumour induction occurs The dose values in Fig 3 are only given as reference values

On the basis of experiments FINKEL et coll (1961 1964) stated that the initial high dose rate immediately after injection is largely responsible for the osteogenic sarcomas that appear many weeks later and that the dose accumulated in the following months from the retained radionuclide is negligible with respect to tumour induction These authors add the reservation however that dose rate alone is not the whole answer and that the contribution of at least part of the integrated dose to tumour induction should be considered when suitable data are available

VAN PUTTEN (1962), on the other hand concluded from his experiments that an evaluation of the relation of total radiation dose and dose rate to tu

mour frequency suggests that the dose rate is not the major determinant of bone tumour incidence. However, this author qualified his statement by saying that the most likely mechanism of bone tumour production seems similar to that found for many cellular effects of radiation where the effects of dose and dose rate are both evident.

The transfer of radiostrontium from mother to foetus is negligible during the first two weeks of gestation and very low during the week before parturition (HOLMBERG et coll. 1960, NELSON et coll. 1965). It appears also from the measurements in the present investigation that no significant difference in excretion rate can be observed between the unmated group and the mated group giving suck during the first three weeks after the administration of radiostrontium. From the beginning of lactation, however, a significant decrease in retention appears. This implies that the dose rates have been practically identical during the first 21 days after administration of radiostrontium. It therefore seems more likely that the decreased tumour rate in the mated group giving suck is connected with the decrease in the accumulated dose which occurs with the lactation. The difference in tumour rate cannot be ascribed to the initial dose rate alone. If the initial dose rate were the determining factor, i.e. the tumour induction occurred during the initial phase, a decrease in the accumulated dose during a later period should not cause a decrease in tumour rate. The accumulated dose therefore appears to be the decisive factor.

The accumulated dose, as a matter of fact, is significantly lower in the mated group giving suck (see Fig. 3) and should be the main cause of the decreased tumour rate in this group. It is, however, not possible to leave out of consideration the significance of an increased resistance against tumour production due to the fact that the lower accumulated dose causes less injury in the hematopoietic tissues.

It can furthermore not be completely excluded that the dose rate may decrease below a certain threshold value, thus giving the tissue a better chance to recover, but this is not a likely possibility.

Acknowledgements

The authors wish to express their sincere thanks to Professor B. Lindell and Docent R. Bjornerstedt for profitable discussions, to Miss E. Engstrom for able statistical assistance and to Miss S. Falk for valuable technical assistance.

SUMMARY

It was shown in an earlier paper that gestation and lactation influence the induction of tumour by ^{90}Sr in mice. The latency period was extended and the bone tumour rate decreased in a mated group giving suck in comparison with an unmated group. In the work now reported

the excretion rates of ⁸⁵Sr in groups of unmated mice only mated mice and mated mice giving suck were investigated The influence of gestation alone was negligible lactation however significantly decreased the retention A relationship between tumour rate and excretion rate in the individual bones was obvious The parameters of the radiation doses influencing the production of ⁹⁰Sr induced bone tumours are discussed

ZUSAMMENFASSUNG

Im ersten Artikel wurde der Einflu s der Gestation und der Laktation auf das Induzieren von Tumoren bei ⁹⁰Sr in Mausen nachgewiesen Die Latenzperiode wurde verlangert und die Anzahl von Skelett Tumoren im Vergleich mit der ungepaarten Gruppe wurde reduziert In der jetzt vorliegenden Untersuchung wurde die Ausscheidungsgeschwindigkeit von ⁸⁵Sr in ungepaarten gepaarten und in stillenden Gruppen von Mausen studiert Der Einfluss der Gestation war sehr gering Wahrend der Laktationsperiode dagegen wurde die Retention signifikant vermindert Korrelation zwischen Tumor Frekvenz und Ausscheidungsgeschwindigkeit in den einzelnen Knochen war deutlich erkennbar Die Parameter der Strahlendosis die den Ursprung von ⁹⁰Sr induzierten Knochen Tumoren beeinflussen werden diskutiert

RESUMÉ

Dans un travail précédent les auteurs ont montré que la gestation et la lactation influent sur l induction de tumeurs par Sr chez la souris Par comparaison avec un groupe de souris non ac ouplées la période de latence est allongée et le taux de tumeurs osseuses est diminué chez les souris qui ont été accouplées et qui allaitent Dans le présent travail les auteurs ont étudié le taux d excrétion de ⁸⁵Sr chez des groupes de souris non accouplees seulement accouplées et accouplées et allaitant L influence de la gestation seule est négligeable mais la lactation diminue de façon importante la rétention de ⁸ Sr Il y a une relation évidente entre le taux de tumeur et le taux d excrétion dans l os Les auteurs étudient les paramètres des doses de radiation qui influent sur la production de tumeurs osseuses dues au ⁹⁰Sr

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FROM NORSK HYDRO'S INSTITUTE FOR CANCER RESEARCH THE NORWEGIAN RADIUM HOSPITAL MONTEBELLO OSLO NORWAY

EFFECT OF SPLENECTOMY FOLLOWED BY CYCLOPHOSPHAMIDE OR TOTAL BODY IRRADIATION ON HEMOPOIESIS IN RATS

by

HERMAN HØST

Although the role of the spleen in hemopoiesis has been studied for many years it is in many respects inadequately understood Thus conflicting data apparently exist on the significance of the spleen in protecting the organism against the toxicity of nitrogen mustards or total body irradiation In mice shielding of the spleen (JACOBSON et coll 1949), as well as splenectomy (MELCHING & MESSERSCHMIDT 1960) reduced the lethal effect of irradiation DEMETZ HERTER & EVANS (1962) found in rabbits that splenectomy protected against the lethal effect of nitrogen mustard while spleen shielding performed by temporary cross clamping of the splenic vessels had no corresponding effect Splenectomy in dogs increased the toxicity of the nitrogen mustard derivative Thio TEPA (HIGGINS FLYNN & GILLESPIE 1964), whereas spleen shielding did not protect against the toxic effect of nitrogen mustard (LEMPERT LEATHER & SCHARFMAN 1963)

The question arises whether the above mentioned apparently conflicting results are in part caused by different effects of irradiation and mustards on

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the spleen This assumption is supported by observations during the last years which suggest that the irradiated spleen may release a mitotic inhibitor (GUNZ 1953, LAMERTON et coll 1960, LAJTHA 1961, MAURICE & JEANRENAUD 1963, LI 1963) Moreover, KLOPFENSTEIN (1963) found that total body irradiation caused less depression of platelets and leukocytes in splenectomized dogs and rabbits than in sham operated controls Corresponding studies in splenectomized animals treated with nitrogen mustard derivatives have not been performed

Differences in the regeneration pattern of hemopoiesis following total body irradiation and cyclophosphamide treatment in rats have been reported (HOST 1966c) The most striking observation was the rapid and complete recovery of myelopoiesis in the cyclophosphamide treated animals, as against the more gradual recovery of myelopoiesis in the irradiated animals The spleen may play a part in this difference in response

The purpose of this paper is to report the hematologic changes after splenectomy, and the effects of the latter on the hematologic response to cyclophosphamide and total body irradiation in rats

Material and Methods Hooded male rats, receiving a standard diet and water ad libitum, were used At the time of splenectomy, the average age was 102 days (80 to 130 days) and the average weight 235 g (200 to 282 g) At the time of treatment (irradiation/injection of cyclophosphamide), 3 to 4 weeks later, the mean weight of the splenectomized rats had increased from 238 to 250 g and that of the sham operated rats from 232 to 250 g Splenectomy was performed under ether anesthesia Sham operation was carried out in the control animals in a similar manner a small piece of omentum being removed instead of the spleen

Preliminary splenectomy studies disclosed that the animals carried a latent *Bartonella muris* infection This latent infection is without significance in normal rats, i e those with an intact spleen Following splenectomy, however, manifest infection with a serious hemolytic anemia may develop To control this infection the animals were deloused and injected intraperitoneally with 6 mg Neosalvarsan (Farbwerke Hoechst AG, Frankfurt) at the time of operation In addition, the animals received Terramycin rubrum (Pfizer, New York) in the drinking water (18 g/50 ml) and they were isolated All the rats recovered promptly from splenectomy and sham operation without suppuration or signs of active *Bartonella muris* infection The latter was evidenced by no deaths and no signs of hemolytic anemia

A total of 122 animals were used in the experiments, half of them being subjected to splenectomy and the others sham operated Three to four weeks

following surgery 5 animals in each of the two groups were sacrificed and examined and served as untreated controls The remaining 56 animals in each of the two groups were divided into two equal groups for irradiation or cyclophosphamide treatment Four rats in each of these 4 groups were sacrificed and examined after 2 4 6 8 10 12 and 14 days The animals were selected at random for the different treatment groups

Cyclophosphamide (Sendoxan Pharmacia Uppsala) was injected into the exposed vena femoralis under ether anesthesia in single doses of 50 mg/kg bodyweight The roentgen dose was 350 R (200 keV, half value layer of 1 05 mm Cu) The treatment procedures have been described previously (Host 1966a)

In the hematologic studies the totals of nucleated marrow cells were counted in samples from the right femur and tibia (Høst 1966b) Smears for differential counts were taken by the brush method (Burke, Brotherstone & Harris 1955) The procedures for the staining of smears and the interpretation and classification of marrow cells have been described in a previous paper (Høst 1966b) The smears for differential counts were coded prior to interpretation to avoid bias One thousand cells were counted in each smear

The peripheral blood studies were performed with samples of freshly flowing blood following amputation of the tip of the tail Erythrocytes and leukocytes were counted with an automatic cell counter (Celloscope Lars Ljungberg Stockholm) Films were stained with May Grunewald and Giemsa for the differential counts of leukocytes in blood One hundred cells were counted in each smear Reticulocytes were stained with 0 5 % brilliant cresyl blue One thousand erythrocytes were counted in each smear by means of Miller s ocular The hemoglobin levels were determined photocolorimetrically as oxyhemoglobin Platelet counts were made by the direct chamber method as described by Brecher Schneiderman & Cronkite (1953)

Results

Effects of splenectomy on hemopoiesis There are discrepancies in the reported hematologic changes following splenectomy especially in erythropoiesis (Lorber 1958 Waldmann Weissman & Berlin 1960) Some of these discrepancies may have been due to species and strain variation in the size of the spleen The effect on hemopoiesis of splenectomy by itself was therefore investigated prior to the study of the splenectomized rats response to cyclophosphamide and to irradiation The data recorded in the Table indicate that the reticulocyte counts were significantly increased in the splenectomized rats as compared to the sham operated rats (0 05 > P > 0 01) whereas the number of red

Table

The effect of splenectomy on peripheral blood values in rats — The values represent the mean of 5 animals with 95 % confidence limits

Treatment group	Reticulocytes (per cent)	Red blood cells ($10^6/mm^3$)	Hemoglobin (g/100 ml)	Platelets ($10^3/mm^3$)	Granulocytes ($10^3/mm^3$)	Lymphocytes ($10^3/mm^3$)
Splenectomized rats	3.18 ± 0.72	8.26 ± 0.70	13.2 ± 1.1	932 ± 17	2.4 ± 1.1	16.4 ± 3.1
Sham operated rats	2.36 ± 0.32	8.40 ± 0.17	14.0 ± 1.1	788 ± 47	1.7 ± 0.6	10.0 ± [illegible]8

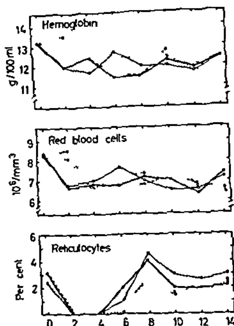
cells and the hemoglobin levels were not significantly reduced. The animals were thus most probably free from the *Bartonella muris* infection, as a severe hemolytic anemia will develop following splenectomy in rats carrying this infection.

The number of platelets was markedly increased (0.01 > P) in the splenectomized rats, a well known finding following splenectomy.

Splenectomy also caused leukocytosis, mainly due to an increase in the number of lymphocytes (0.01 > P). A slight upward trend was also observed in the number of granulocytes following splenectomy (0.1 > P > 0.05). The changes observed in the white blood cells following splenectomy are consistent with those reported by e. g. PALMER et coll. (1951).

Counts of total nucleated cells revealed a higher cell content in the bone marrow of the splenectomized animals (P = 0.05). The mean number was 2 133 000 nucleated cells pr mg (2 055 000 to 2 270 000) as compared with 1 927 000 (1 799 000 to 2 071 000) in the sham operated group. All the different marrow cell types contributed to this increase in total nucleated marrow cells. The increase, however, was significant only as regards the erythroid cells (0.05 > P > 0.01). These cells increased from 471 000 (422 000 to 549 000) per mg bone marrow to 577 000 (515 000 to 620 000) following splenectomy.

Effect of cyclophosphamide or irradiation on splenectomized rats. The results presented in Fig. 1 indicate that the reticulocytes were reduced to zero in all treatment groups from the 2nd to the 4th day. Rapid and apparently complete recovery occurred in the course of the following days. The reticulocytes temporarily exceeded the initial values in the cyclophosphamide treated animals, whereas the number remained within the normal range in the irradiated animals. These findings are in agreement with previous ones on bone marrow



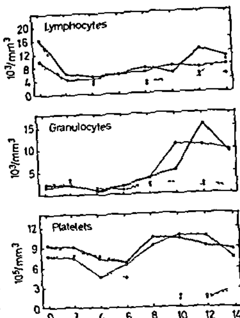


Fig 1 Comparative effects of cyclophosphamide and total body irradiation on peripheral erythroid values of normal and splenectomized rats

Fig 2 Comparative effects of cyclophosphamide and total body irradiation on lymphocytes granulocytes and platelets in peripheral blood of normal and splenectomized rats

●———● cyclophosphamide and splenectomized ●– – –● irradiated and splenectomized ——— cyclophosphamide and sham-operated ○ ○ irradiated and sham operated

which revealed that erythropoiesis is extremely sensitive to both irradiation and cyclophosphamide (Host 1966c) The transitory halt in erythropoiesis caused no significant anemia but the number of red blood cells as well as the hemoglobin levels decreased slightly

The number of platelets was markedly reduced in all the treatment groups on the 4th and the 6th day compared with the pre treatment levels as shown in Fig 2 The number of platelets in the irradiated animals fell further to about one third of the initial values and remained at this level during the rest of the observation period Recovery to normal levels in the cyclophosphamide treated animals on the other hand occurred in the course of the 6th to 8th day this is consistent with previous observations in animals (Lane

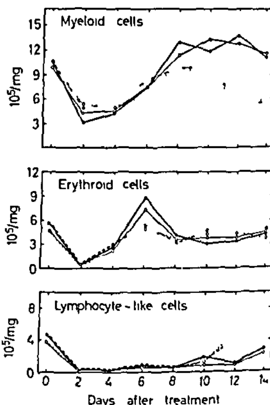


Fig 3 Comparative effects of cyclophosphamide and total body irradiation on marrow cells in normal and splenectomized rats ●———● cyclophosphamide and splenectomized ●– – –● irradiated and splenectomized ——— cyclophosphamide and sham operated ○ ○ irradiated and sham operated

1959) and in human subjects (NISSEN MEYER & HOST 1960), and suggests that cyclophosphamide has little injurious effect on the megakaryocytes

As mentioned above, the platelet counts prior to treatment were significantly higher in the splenectomized than in the sham operated animals After irradiation as well as after cyclophosphamide treatment this difference seemed to disappear

The data in Fig 2 indicate that the granulocyte response to cyclophosphamide or irradiation was unaffected by splenectomy or sham operation Moreover, the trends observed were the same as those in the author's previous studies

The pre treatment difference in lymphocyte values between splenectomized and non splenectomized animals tended to disappear both after irradiation and cyclophosphamide treatment but reappeared at the end of the observation period

The effects of treatment on the different types of marrow cells are demonstrated in Fig 3 Neither in the irradiated nor in the cyclophosphamide treated animals had splenectomy any influence on the regeneration pattern of the different marrow cells The regeneration of the erythroid cells was

apparently the same after irradiation and following cyclophosphamide as previously reported by the author Differences in the regeneration pattern of both the myeloid and the lymphocyte like cells were however evident after the two types of treatment

Discussion

Effects of splenectomy on hemopoiesis The present data indicate that splenectomy caused reticulocytosis without any signs of anemia WALDMANN WEISSMAN & BERLIN (1960) have demonstrated that the reticulocytes have an increased intravascular life span in splenectomized dogs which may be explained in different ways Thus LORBER (1958) reported that in splenectomized animals the reticulocytes are released at an earlier stage of development than in normals Furthermore CROSBY (1959) has suggested that the normal spleen traps the reticulocytes and pits the red cells of their intracellular inclusions Loss of the spleen may thus delay the disappearance of the reticular chromatin

Thrombocytosis and leukocytosis are common findings following splenectomy The life span of platelets has been found to be the same in normal splenectomized and hypersplenic rats (HJORT & PAPUTCHIS 1960) It is therefore supposed that the spleen influences the rate of production rather than the rate of destruction of the platelets PALMER et coll (1951) reported that the spleen also exerts an effect on the rate of production or liberation of leukocytes from the bone marrow

The present study indicates an increase in the number of erythroid marrow cells at 3 to 4 weeks following splenectomy whereas BIERRING & GRUNNET (1964) in rats found an increased number of marrow lymphocytes 60 days after splenectomy These investigators used young rats weighing about 75 g while in the present experiments the rats weighed about 235 g and were about 100 days old The discrepancy between the finding in the present study and that of BIERRING & GRUNNET may be due to the changing cellular distribution in bone marrow of young growing rats (HARRIS & BURKE 1957)

Effects of cyclophosphamide or irradiation on splenectomized rats Splenectomy seemed to have no influence on the regeneration pattern of hemopoiesis neither in the irradiated nor in the cyclophosphamide treated animals Thus an eventual spleen factor cannot explain the different patterns of marrow cell regeneration observed in the irradiated and cyclophosphamide treated animals (HOST 1966c)

The apparently confusing results obtained in previous studies by spleen shielding in reducing the lethality of radiation or mustards probably depend

as much upon species differences as upon variations in the type of treatment (JACOBSON et coll, DEMETZ et coll and LEMPERT et coll) The observations of JACOBSON et coll in mice of the protective effect of spleen shielding has thus not been duplicated in other species (LILLEHEI, LONGERBEAM, SADEK & YUNIS 1960) This suggests that the spleen may be a more important factor hematopoietically in mice The protective effect in mice of spleen shielding (JACOBSON et coll 1949) as well as of splenectomy (MELCHING & MESSERSCHMIDT) in reducing the lethal effect of irradiation is however not easy to reconcile

The origin of the lymphocyte like marrow cells has been the subject of extensive investigations Some authors have suggested that these cells are extramedullary in origin, and that they arrive from the blood stream into the bone marrow where they may act as potential stem cells (FARR 1951, YOFFEY 1960, HARRIS 1961) This interpretation of their origin has however been disputed (TROWELL 1958, LOUTIT 1960, GESNER & GOVANS 1962, OSMOND & EVERETT 1964) The present observations indicate that splenectomy had no influence on the regeneration of the lymphocyte like cells neither in irradiated nor in cyclophosphamide treated animals If the lymphocyte like marrow cells originate from extramedullary lymphoid tissue, the spleen may therefore be excluded as an important source of such production

Acknowledgements

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SUMMARY

The regeneration of hemopoiesis following total body irradiation or cyclophosphamide has been studied in normal and splenectomized rats Splenectomy performed 3 to 4 weeks prior to treatment had no influence on the regeneration pattern of the hemopoiesis It appears that the different patterns of regeneration following the two types of treatment cannot be caused by a spleen factor

ZUSAMMENFASSUNG

An normalen Ratten und an Ratten nach Milzexstirpation wurde die Regenerationsfähigkeit der Hamatopoese nach Totalbestrahlung und nach Cyclophoshamidverabreichung studiert Die Milzexstirpation welche 3 bis 4 Wochen vor der Behandlung vorgenommen wurde hatte keinen Einfluss auf das Verhalten der Regeneration des hamatopoetischen Gewebes Es kann angenommen werden dass die Milz keinen Einfluss auf die Hamatopoese nach den beiden *Behandlungsmethoden hat*

RÉSUMÉ

La régénération de l'hématopoiese après irradiation totale du corps ou apres cyclophosphamide a été étudie sur des rats normaux et splénectomisés. La splénectomie pratiquée 3 a 4 semaines avant le traitement n'a pas d'influence sur la type de la régénération de l'hématopoiese. Il semble que les différents types de régénération observés après ces deux types de traitement ne sont pas déterminés par un facteur splénique.

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FROM THE RADIOTHERAPY DEPARTMENT AT THE UNIVERSITY OF MARYLAND HOSPITAL BALTIMORE U S A

A VARIABLE ELECTRON BEAM COLLIMATOR FOR A MEDICAL BETATRON

by

J EUGENE ROBINSON and R S McDOUGALL

The design and construction of collimating devices for high energy electron beams for use in radiotherapy has been a subject of considerable interest during the last few years LAUGHLIN et coll (1953 1954) have reported on the construction and use of fixed collimators and lucite cones to define the treatment field The Brown Boveri Corporation has designed and constructed fixed lucite cones which are standard equipment on their medical betatrons These cones are flared to approximate the spread of the beam DAHLER (1965) has reported considerable improvement in the electron beam isodose distribution by the use of brass cones He indicates similar improvement with lucite cones not flared but with sides parallel to the beam central axis having brass strips on the terminal end *LOEVINGER et coll (1961) have re* ported the use of lucite cones with lucite or lead internal defining blocks BRADSHAW et coll (1964) have reported studies in which they explored the effect on the isodose shape when various fractions of the electron beam were caused to strike the sides of dural defining cones They were able to improve

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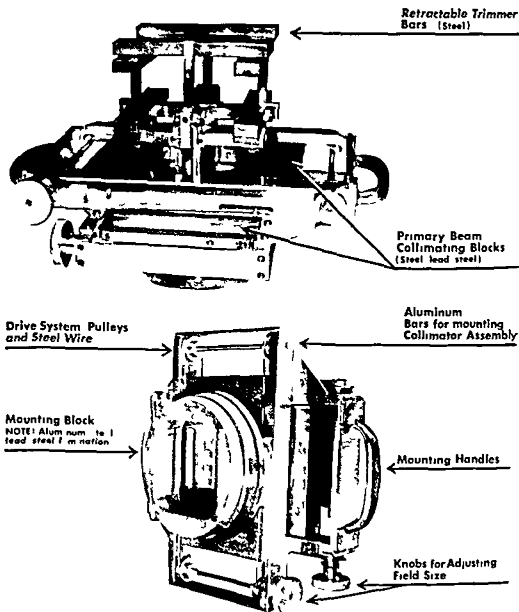


Fig 1 Rear view of collimator showing mounting block (top view) and side view of the collimator (lower view)

the isodose distribution by using a defining system in which an optimum fraction of the electrons scatter from the sides of the cones

To our knowledge all of these defining systems have used fixed collimators and cones This necessitates a large number of different cones to provide collimation for the range in field sizes required by the radiotherapist for patient treatment The construction of these collimators and cones requires the

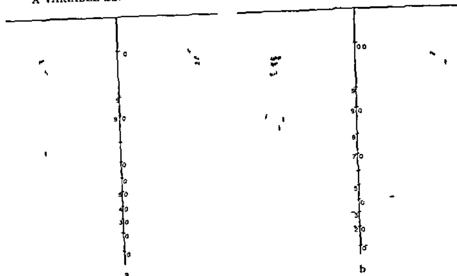


Fig. 2 a) Isodose curves with 35 MeV radiation obtained with a Brown Boveri fixed cone b) Isodose curves obtained with 35 MeV radiation and a variable collimator

skill of a competent machinist and since the therapist requires a great variety of sizes and shapes there is considerable expense involved in developing a suitable set Even with the availability of a great variety in cone sizes, the therapists are continually being plagued by the need for the field sizes 1 cm smaller or 1 cm larger than those available The great variety of cones required, creates not only a financial problem but a problem in storage Also in a busy therapy department much time is wasted in the removal and replacement of the cones required for different patients

During the past two years the Radiotherapy Department at the University of Maryland Hospital has been in the process of developing an electron beam radiotherapy program using a Brown Boveri 37 MeV betatron As part of this program a project was initiated to design and construct a suitable variable collimating system In designing this system we felt that the possible use of fixed collimators of the types supplied by the Brown Boveri Corporation should not be completely abandoned Therefore the design should include the possibility of interchanging the fixed collimators with the variable collimating system To make this possible the mounting assembly for the variable system was centered around mounting blocks identical to those used by this company for their fixed cones

The base of the Brown Boveri cone which acts as the primary absorber and mounting block is circular in cross section and is tapered to fit into a

collimator housing on the face of the machine. This block is a laminated structure, made up of layers of aluminium, lead and steel, which provides the proper shielding and minimizes brehmsstrahlung production.

Our collimator structure was then built on and supported by a tapered circular laminated section consisting of 2 cm of aluminum, 1.5 cm of stainless steel and 0.5 cm of lead. It is circular in cross section with a diameter of 17.5 cm on the forward end, tapering to 15.8 cm. An opening is machined in the center, corresponding to the largest field sizes in use (14 × 14 cm) projected back to that position. The collimator proper consists of two pairs of primary beam shutter blocks, also *laminar in structure, with 2 cm of stain*less steel and 0.6 cm of lead. These blocks are supported by nylon bearings, which roll along slots and guide tracks, mounted normal to the central beam axis. They are driven from control knobs by a pulley and cable system. Two sets of trimmer bars (see Fig. 1) are mounted on the outside of these blocks. The second set can be retracted or extended to accomodate to irregular patient contours. These extendable trimmer bars have a dual purpose: they allow field trimming close to the patient's skin, and are an in field localization. Spring loaded balls and detents are used to secure them in specific positions.

As an aid in field localization a retractable, wide beam light system is housed in the collimator support structure. At the present time, no attempt has been made to duplicate exact focal spot skin distances with this light source, but with the trimmer bars extended close to the patient's skin, the light field duplicates the size of the radiation field with sufficient accuracy. At a later period, when it becomes necessary to replace the betatron accelerator tube, a *light system which does duplicate exact focal spot skin distance* and field spread, will be incorporated into this system.

Isodose curve measurements have been made both with this variable collimator, and with the fixed cones supplied by the Brown Boveri Corporation. A comparison (see Fig. 2) shows very similar distributions *from the* two collimation systems, with perhaps less penumbra with the variable collimator. The central axis depth dose curves are almost identical. To check for possible leakage outside the field proper, extensive measurements were made and no stray radiation was detected. Roentgen ray contamination of the electron beam with the variable collimator was identical to that measured with fixed cones (approximately 4 % to 5 %).

The collimator and support structure weighs approximately 30 pounds. To facilitate mounting of the collimator, two handles are located on the sides. The unit can be easily mounted and dismounted by a medical technician. In practical use, it has been found to be convenient and to result in considerable saving in patient set up time.

SUMMARY

A variable collimator for electron beam therapy has been designed and constructed for a 37 MeV Brown Boveri betatron It is physically interchangeable with fixed cones supplied by the manfacturer and gives comparable beam definition No stray radiation was detected outside of the beam and roentgen ray contamination was identical to that found with fixed cones It is a convenient and time saving device in the clinical use

ZUSAMMENFASSUNG

Ein variabler Kollimator für Elektronenstrahlen Therapie mit dem 37 MeV Brown Boveri Betatron wird beschrieben Dieser Kollimator kann gegen den vom Hersteller gelieferten Konus ausgewechselt werden und man erhalt eine vergleichbare Definition des Strahlen bundels Keine Streustrahlung ist konstatiert worden und die Rontgenstrahlen Kontamina tion war dieselbe wie fruher In der Klinik ist dieser Kollimator eine praktische und zeitspa rende Vorrichtung

RÉSUMÉ

Les auteurs ont conçu et fait construire un collimateur variable pour le traitement par un faisceau d électrons avec le bétatron de 37 MeV Brown Boveri Il est physiquement équivalent aux cones fixes fournis par le fabricant et donne une définition du faisceau comparable On n a pas détecté de rayonnement dispersé hors du faisceau et la contamination de rayons roentgen est identique a celle que causent les cones fixes Pour l usage clinique ce dispositif est commode et fait gagner du temps

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DOSIMETRY OF HIGH-ENERGY ELECTRON RADIATION BASED ON THE FERROUS SULPHATE DOSIMETER

by

C PETTERSSON and G HETTINGER

Dosimetry of high energy radiation from accelerators is not as well founded as from ^{60}Co gamma rays and conventional roentgen rays In spite of the fact that the number of accelerators for medical treatment and biologic investigations is continually increasing, no standardization laboratory has as yet undertaken calibrations of practical dosimeters for high energy electron radiation With different dosimetric units and concepts, the comparison between treatment methods and results becomes difficult The results also from radiobiologic investigations may be difficult to interpret if the dose units are not in accordance with the recommendations of the ICRU For most betatron laboratories it is too laborious to develop calorimetric methods for the absolute determination of absorbed radiation energy

When measuring doses with the ferrous sulphate dosimeter, it is possible to obtain the values in absolute units with the aid of a standard equipment for chemical analysis This can be done independently of calibrations from a standardization laboratory by using values given in the literature for the

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characteristic constants of the dosimeter: the G value, and the molar extinction coefficient. In our opinion this dosimeter is at present the most convenient substitute for a standard dosimeter at high-energy electron radiation in the dose range 4—40 krad.

The aim of the present paper is to report on the use of the ferrous sulphate dosimeter for the determination of absorbed doses from 10 to 30 MeV electron radiation. A survey of current literature is presented, factors affecting the response of the dosimeter and the possibility of using the instrument as a transportable intercomparison dosimeter are also discussed.

Only a few accelerator stations have based dosimetry of high energy electron radiation solely on the ferrous sulphate dosimeter (LOEVINGER et coll. 1961, BARR et coll. 1961 and DUTREIX & DUTREIX 1965). Extensive material has been published on the performance of this dosimeter system. Using the new accurate determinations of the G value as a basis it should now be possible to calibrate monitors and other practical dosimeters with an uncertainty of a few per cent only. Besides good reproducibility the qualities which render it specially convenient for this purpose are: (1) independence of electron energy in the range considered in this paper, (2) independence of dose rate up to about 10^6 rad/sec pulsed radiation, (3) the dose determinations are independent of calibrations from a standardization laboratory, (4) the fact that apart from the spectrophotometer only simple equipment is needed.

Description of the dosimeter

The dosimeter solution consists of small quantities of ferrous sulphate or ferrous ammonium sulphate and sodium chloride dissolved in 0.8 N sulphuric acid. This solution is very nearly water equivalent at high electron energies and ^{60}Co gamma rays. When exposed to radiation part of the ferrous ions are oxidized to ferric ions (FRICKE & MORSE 1929). The quantity of ferric ions is usually determined photometrically (HARDWICK 1952) by measuring the light absorption at a wave length of 304 nm, where the absorption spectrum has a maximum.

The read absorbance is related to the absorbed dose through the following equation

$$D_d = \frac{9.65 \cdot 10^8}{G_t \cdot \varepsilon_t \cdot \delta \cdot d} \Delta A_t \tag{1}$$

where D_d = absorbed dose in the dosimeter solution (rad)

ΔA_t = difference in absorbance between irradiated and unirradiated solution at temperature t (O.D.U.)

d = optical path length of the photometer cell (cm)

ε_t = molar extinction coefficient for ferric ions at temperature t (liter mol^{-1} cm^{-1}),

G_t = number of ferric ions produced per 100 eV absorbed in the dosimeter solution at irradiation temperature t,

δ = density of solution (g/ml)

The factor 9 65 10^8 converts the dose into units of rad

The molar extinction coefficient ε_t is almost entirely dependent on temperature t in the photometer measurements On the other hand, the chemical yield during irradiation, the G-value, can be affected by several factors, as, for instance, the composition of the dosimeter solution, the wall material in the irradiation cells, temperature at irradiation, impurities and storage time It is necessary, and also possible, to control all these variables by a careful technique

G value and molar extinction coefficient The G value and the molar extinction coefficient together form the calibration of the dosimeter G values for electron radiation from accelerators have been published, they are assembled in Table I, which also includes G values for ^{60}Co gamma rays The calorimetrically determined values are lower than those based on ionization chamber dosimetry The mean, without considering this discrepancy, is 15 59 $(100\ eV)^{-1}$, with a standard error of less than 1 % Systematical errors in one or both calibration methods should probably be taken into account The error of the mean value is expected to be less than between 2 % and 3 % G values determined in the same laboratory, but at different energies, show no or little dependence on energy The energy dependence is probably negligible in the energy range 10—30 MeV (ZSULA et coll 1957, and MARKUS 1964)

As regards the influence of the temperature of the solution during irradiation, different results ranging from 0 0 to + 0 4 % per degree Celsius have been reported (MINDER & LIECHTI 1946, DEWHURST 1949, HARDWICK 1953, *SCHWARZ 1954, HOCHANADEL & GHORMLEY 1962,* and *LIESEM & POHLIT* 1962) Our experiments show that the varying results may be due to the influence of the wall material in the irradiation cells With irradiation in polystyrene cells (4 ml) and polyethylene cells (3 5 ml), a temperature coefficient of, respectively, + (0 11 ± 0 07), and + (0 14 ± 0 07) per degree Celsius was obtained in the temperature range 15—30° C In the temperature range 30—45° C, on the other hand, a temperature coefficient per degree Celsius of + (0 38 ± 0 11) was obtained with polystyrene cells and — (0 11 ± 0 11) with polyethylene cells Unfortunately, the G values in the literature are almost always given without any statement about temperature In our laboratory, the G value determinations for high energy electron radiation and

Table 1

G values of the ferrous sulphate dosimeter with high-energy electrons and Co gamma rays Composition of dosimeter solution in most experiments 10^{-3} M ferrous sulphate 10^{-3} M sodium chloride in 0 4 M (0 8 N) sulphuric acid

Type of rad ation	Method	G value $(100\ eV)^{-1}$	Irradiat on temperatur C	
Electrons 2 MeV	Charge nput	15 45±0 30		a
15	Calorimetry	15 ? ±0 4		b
10	»	15 32±0 34		c
20	»	15 17±0 ?8		c
20	»	15 56±0 12	25 0±0 5	d
10	Ion at on	15 7 ±0 3		e
30	»	16 3 ±0 3		e
17	»	15 8 ±0 4	25	f
20	»	16 0 ±0 4	25	f
25	»	15 9 ±0 4	25	f
	Weighed mean	15 59±0 10		
Co gamma rays	Calorimetry	15 6 – 15 8		g
	»	15 42±0 04		h
	Io izatior	15 40±0 25		h
	Calor metry	15 57±0 14	25 0±0 5	d

References a) SCHULER & ALLEN 1956 b) ANDERSON 1962 c) GEISSELSODER et coll 1963 d) PETTERSSON (to be publ shed)) MINDER 1961 f) LIESEM & POHLIT 1962 g) ICRU Report 10 b (196?) h) DAVIES et coll 1963 b

• Co gamma rays were performed at a temperature of (25 ± 0 5) C (PETTERSSON to be published) When the measurements are made in a water phantom the temperature is kept at about 25° C When and if temperature corrections are needed a temperature coefficient of + 0 15 % per °C is employed which is the mean value of the temperature coefficients published

The concentration of ferric ions is most conveniently determined photometrically by measuring the absorbance at 304 nm or at 224 nm The sensitivity of the dosimeter is approximately doubled when the measurements are carried out at the latter wave length (SCHARF & LEE 1962) Solutions irradiated in polyethylene or polystyrene cells have shown an increased absorbance at this wave length even when a correct result was obtained at a wave length of 304 nm The absorption spectra in Fig 1 show this effect after extremely long storage time Therefore when accuracy is required a wave length of 304 nm should be employed

The molar extinction coefficient of the ferric ions at 25 C in 0 8 N H_2SO_4 can be equalled to 2 194 liter mol^{-1} cm^{-1} which is the mean value of several

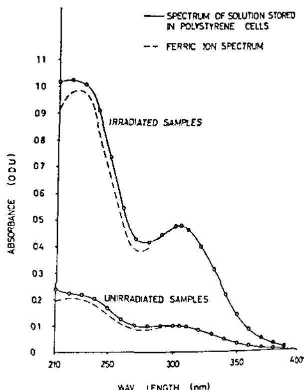


Fig 1 Absorption spectrum of dosimeter solution stored for 3 weeks in polystyrene cells compared to a ferric ion absorption spectrum Extraneous absorbance shows up in dosimeter solution at the 224 nm absorption maximum

determinations at 304 nm put together by SCHARF & LEE (1962) The variations from one photometer to another seem to be small In our test of three photometers (Beckman DU), results consistent within ± 0 5 % were obtained A similar result has been reported by SHALEK et coll (1962) in a test of four photometers of the same make The extinction coefficients given by SCHARF & LEE agree within about ± 1 %

The molar extinction coefficient is relatively strongly temperature dependent, with a temperature coefficient of + 0 7 % to + 0 8 % per °C (BASTIAN et coll 1953, LIESEM & POHLIT 1962, and SCHARF & LEE 1962) If the cell compartment of the photometer is not temperature stabilized, the temperature should be measured directly after the measurement and a correction to 25° C be made

Calculation of dose in water from read absorbance With a G value of 15 6 (100 eV)$^{-1}$, $\varepsilon = 2\ 194$ liter mol^{-1} cm^{-1} and $\delta = 1\ 024$ g/ml, the following correspondence between absorbance and dose in the dosimeter is obtained

$$D_d = \frac{2\ 76\ 10^4}{[1+0\ 0015\ (t-25)]\ [1+0\ 007\ (t-25)]}\ \Delta A_t \text{ rad} \qquad (2)$$

where

D_d = absorbed dose in dosimeter solution (rad),

ΔA_t = difference in absorbance between irradiated and unirradiated solution at temperature t C the optical path length = 1 cm, and

t = temperature during irradiation (C)

At high electron energies the mass stopping power ratio between water and dosimeter solution is 1 004, and so the dose in water is

$$D_w = 1\ 004\ \ D_d \tag{3}$$

where D_w = absorbed dose in water (rad) and D_d = absorbed dose in dosimeter solution (rad)

Preparation of dosimeter solution The ferrous sulphate dosimeter consists of 1 mM ferrous sulphate or ferrous ammonium sulphate and 1 mM sodium chloride dissolved in 0 4 M (0 8 N) sulphuric acid For ten liter dosimeter solution 3 92 g ferrous ammonium sulphate 0 59 g sodium chloride and 220 ml concentrated sulphuric acid are needed Deviations from the mentioned quantities only slightly influence the response of the dosimeter An accuracy of 10 % is sufficient to give a reproducibility > 1 % The chemicals must be of analytical reagent grade and the water must be distilled at least once Sodium chloride is added to eliminate influence from saturated organic impurities mainly found in the water (DEWHURST 1951) or introduced through contact with the irradiation cells (WEISS et coll 1956)

Influence from impurities in the sulphuric acid has also been noticed (DAVIES & LAW 1963) and cannot be eliminated by adding sodium chloride A decrease in response with up to 3 % may occur with certain brands of sulphuric acid even of analytical reagent grade The sulphuric acid to be used should consequently be tested by pre irradiation with a few krad (DAVIES & LAW 1963) The pre irradiation must be performed in the presence of H_2O and the concentrated acid should therefore be diluted to e g 2 N To avoid high blank readings the ferrous sulphate and the sodium chloride should be added only after the pre irradiation The influence of impurities may be studied by irradiation of dosimeter solutions prepared from pre irradiated and non pre irradiated sulphuric acid respectively In our examinations with a brand (Merck) of sulphuric acid from three deliveries we obtained too low values before pre irradiation the values being respectively 0 1 % 0 2 % and 0 4 % lower

The dosimeter may conveniently be stored as a stock solution The chemicals mentioned above are then dissolved in distilled water to provide 1 liter Immediately before use one part of stock solution is diluted in 9 parts of distilled

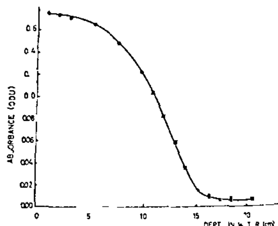


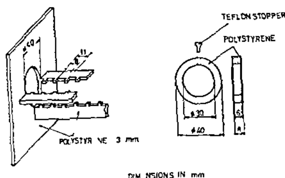
Fig 2 Depth dose curve at 33 MeV electrons dosimeters at all depths (○) dosimeters only at depths of 10 cm and more (×) The depth dose curve is not affected by the dosimeters

water Every week a new stock solution should be prepared but the storage time is not critical since the spontaneous oxidation is slow (HUFFMAN & DAVIDSON 1956), such oxidation is moreover eliminated by keeping a non irradiated dosimeter solution as photometric reference When small quantities of solution are stored in vessels of large volume, however, an increased oxidation rate has been reported (PRIBICEVIC et coll 1961)

Storage vessels should be made of borosilicate glass, such as Pyrex or Jena All glassware to be used for the preparation and storage of dosimeter solutions should be cleansed with strong sulphuric acid and rinsed with distilled water When chromic acid is used, it has been found necessary carefully to rinse at least 10 times with distilled water to prevent false photometer readings

Other sulphuric acid concentrations are sometimes used but most examinations with the ferrous sulphate dosimeter have been made with solutions of normality 0 8 Preliminary studies have indicated that it is an advantage to use 0 1 N solution since then the effects of storage in dosimeter cells made of polystyrene will be less marked The G value for a 0 1 N dosimeter solution is however not as well known as for 0 8 N Our determinations with 20 MeV electron radiation and ^{60}Co gamma rays (PETTERSSON, to be published) have given about 2 % lower G value for a 0 1 N solution This result agrees with the one reported by ALLEN et coll (1957)

Irradiation cells For the irradiation cells different laboratories have used polystyrene, polyethylene, teflon, quartz, polypropylene, perspex, and other materials Two factors should be considered in the choice of the material The dosimeters must not distort the radiation field to be measured, this is especially important in the determination of depth dose curves when a great number of dosimeters are placed in succession, one after the other along the



F g 3 Polystyrene irradiation cell and cell holder The cells are made of transparent unplasticized poly styrene (HI Impact Polystyrene Sheets Formulation 475 manufac tured by Colonial Kolonite Co Chicago USA) The circular discs are glued to the ring by means of polystyrene d ssolved in amyl ace tate

central axis Further the cell material must not influence the chemical yield during irradiation

On the other hand the boundary effect between wall and dosimeter solu tion as a result of electronic non equilibrium conditions is of no vital im portance at high electron energies Roughly two thirds of the absorbed dose is delivered directly by the primary electrons according to data given by MARKUS (1964) Furthermore when plastic cells are used energetic secondary electrons generated in the wall do not disturb the dose distribution in the fer rous sulphate solution

Such boundary effects have been observed at °Co gamma radiation with cylindrical glass cells when the internal diameter was diminished to less than 8 mm but not with polystyrene cells (WEISS et coll 1956) These effects may presumably arise due to the fact that more secondary electrons per unit area escape from the gla s wall than from the polystyrene wall This assumption may be verified by calculations based on mass energy absorption coefficients and the mass stopping powers of the different materials

Cells for depth dose measurements may conveniently be made of poly styrene which is a very nearly water equivalent material (LOEVINGER et coll 1961) Used together with a 0 8 N ferrous sulphate solution a dosimeter system which does not appreciably affect the radiation field may be obtained The depth dose curve for 33 MeV electron radiation agrees in its latest part with the values obtained when the dosimeters were placed only at the depths of 10 cm or more as may be seen from Fig 2

The shape of the cells is shown schematically in Fig 3 Unplasticized poly styrene was used Walls of 1 mm thickness are glued on to a ring of polystyrene 6 mm thick The glue is a solution of polystyrene in amyl acetate No glue surplus must be allowed to find its way to the measurement volume because

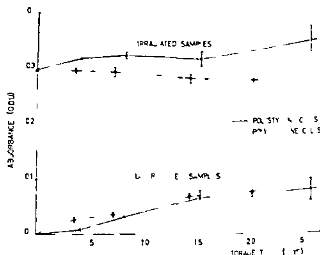


Fig 4 Effect of storage of dosimeter solution in plastic irradiation cells The dosimeters were irradiated at the middle of the storage period Absorbances of irradiated samples are corrected by subtracting absorbances of unirradiated samples stored for the same length of time Polystyrene causes an increased response whereas *polyethylene gives* a slowly decreasing response

then the response of the dosimeter is affected in a considerable degree After gluing on, the cells are vacuum dried for about 24 hours, preferably under heat (maximum temperature 60° C) They are thereafter cleansed with a detergent, rinsed several times in distilled water, and then filled with dosimeter solution

*Most plastics increase the response of the dosimeter or they cause meas*urable optical absorbance even without irradiation, if no special precautions are taken to prevent these effects To improve the reproducibility and obtain accurate measurement results, several methods of treating the plastic cells have been tried CORMACK et coll (1954) suggested repeated pre irradiations with dosimeter solution or with water in the cells, until the response of the dosimeter became stable SINCLAIR (1963) has proposed storage of the dosimeters for 24 hours, followed by pre irradiation with at least 10 krad immediately before measurements are to be performed GLOCKER et coll (1958) reported improved reproducibility solely through pre irradiation of the dosimeters immediately before taking them into use LOEVINGER et coll (1961) reported that a thin coating of ceresine wax eliminated the chemical wall effect in polystyrene cells

In our experience the simplest method is to store the polystyrene cells, filled with dosimeter solution, for about two days before the first irradiation is to take place, and then to rinse them repeatedly with fresh dosimeter solution After such a treatment we have found several series of newly manufactured cells to function satisfactorily at the first irradiation When dosimeter cells are used daily they can be stored filled with dosimeter solution between the irradiations Immediately before irradiation they must however be rinsed two

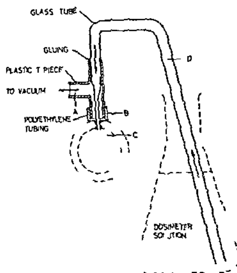


Fig 5 Vacuum filling device When flange B is pressed against the photometer or irradiation cell C vacuum causes the dosimeter solution to fill the cell through tube D

to three times with fresh solution With longer intervals between irradiations the dosimeter solution should be changed at least once a week

Some dosimeters should be left unirradiated and read at each examination together with the irradiated ones If measurable absorbance is obtained with the unirradiated dosimeters a correct result cannot be obtained by applying the difference between the absorbance in, respectively, the irradiated and un irradiated solutions The observation has namely been made with polystyrene cells that as soon as a measurable absorbance was found in the controls the exposed dosimeters showed an increased response The effect is of no impor tance with normal irradiation times because it does not appear until the storage time amounts to about 2 hours The influence of extreme storage times is demonstrated in Fig 4 On the one hand the absorbance of the controls in creases with storage time and on the other hand the response of the dosimeter increases even after correction for the absorbance of the controls Pre irradia tion with doses up to 0 5 Mrad left these effects unchanged

The situation is different with polyethylene cells (about 3 5 ml) Also wit these cells absorbance occurs in the unirradiated solution after an hour o after a couple of hours but after correction for this the response is made in dependent of storage time for up to a week then the response may decreas somewhat (Fig 4) With polyethylene cells of somewhat larger size KRETSCHK 1965) found the response to be independent of storage time for up to 3 week

The fact that a measurable absorbance occurs in an unirradiated solutio has generally been attributed to spontaneous oxidation of ferrous ions Th

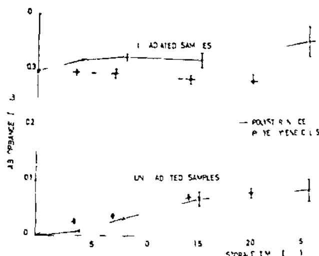


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Table 2b

Dosimeters irradiated in Helsinki and evaluated in Umeå time for transport to and from Helsinki about 60 hrs irradiations were performed approximately at the middle of this time interval

Electron energy MeV	34	21	15
Estimated absorbed dose in water Helsinki	6 000 rad	5 400 rad	5 400 rad
Absorbance at evaluation in Umeå O D U	0.235	0.208	0.214
Corrected for zero dose reading O D U	0.231	0.204	0.210
Corrected for increased yield due to storage (−2.8) O D U	0.225	0.198	0.204
Calculated absorbed dose in water rad	6 130	5 390	5 560
Deviation from estimated value	+2.2	−0.2	+3.0

The geometrical slit should be kept as narrow as possible since a spectral slit of too great a width also leads to error The photometer then integrates light also from parts of the spectrum next to its maximum which yields too low readings

A pair of matched quartz cells are generally used in the photometer measurements One contains a reference solution preferably unirradiated dosimeter solution and by the other one the irradiated solution is measured The matching is controlled before and after each series of measurements by comparing the two cells with fresh dosimeter solution in both If the cells differ in absorbance the difference is applied for correction of the actual measurements

The reproducibility of the photometrical recordings is greatly improved if the cells after matching are not taken from, or displaced in the cell holder The cleansing of the outer face of the cells has also been found to be less critical with this procedure

The accuracy of the photometrical readings can be further improved if a small amount of the solution to be measured is used for rinsing the photometer cell after a previous measurement

As has been mentioned earlier, the deviations in calibration of most photometers seem to be small and they usually fall within the limit of measurement accuracy It therefore does not seem necessary to calibrate the photometer for use in ferrous sulphate dosimetry A standard solution of ferric ions is however easy to prepare by the following method

An amount of 0.1607 g Fe_2O_3 analytical reagent grade (99.4 %) is dissolved in 5 ml concentrated hydrochloric acid in a large test tube The hydrochloric acid is made to evaporate by adding concentrated sulphuric acid and thereafter more H_2SO_4 to make a total of 44 ml is added A volumetric flask

Table 2a

Evaluation of the control dosimeters in Umeå

	Dosimeters stored in Umeå	Dosimeters sent to and from Helsinki
Zero dose reading after 60 hrs storage O.D.U.	0.004 ± 0.003	0.004 ± 0.002
Control runs with ^{60}Co in Umeå before transport	0.353 ± 0.003	0.353 ± 0.003
Dito after transport 60 hrs	0.372 ± 0.002	0.373 ± 0.003
Increased yield due to storage %	+5.4	+5.7

spectra of a dosimeter solution kept for about 3 weeks in polystyrene irradiation cells are shown in Fig. 1, and may be compared with the ferric ion spectra measured with the same photometer. It may be observed that other optically active substances, apart from the ferric ions, are present in the solution.

If measurements are to be made only at the dose maximum of the electron beam, dosimeter cells of polyethylene may be preferred since capped tubes are commercially available. Polyethylene is almost water equivalent and can be used at longer irradiation times because of its better storage qualities. Cleansing with a detergent, rinsing with dosimeter solution and storage for a day or two with dosimeter solution is recommended before it is first taken into use.

The ageing procedure becomes more critical with small volumes. SEHESTED et coll. (1963) have reported that the response of the ferrous sulphate dosimeter, both with glass and polyethylene cells, increases with more than 1 % per cm^{-1} with increasing surface to volume ratios. We have observed no effects of this magnitude after ageing of the polystyrene as described in this paper. With a variation of the surface to volume ratio from 4 cm^{-1} to 20 cm^{-1}, no change in the response has been noticed for high energy electrons (SVENSSON *et coll.*, to be published).

Photometer measurements and calibration procedures

For the photometrical analysis of the dosimeter, a spectrophotometer, provided with a hydrogen or deuterium lamp and photomultiplier, and furnished with temperature stabilization for the cell compartment, is generally used.

By measuring the spectrum of the ferric ions, the position of the absorption maximum can be determined, after which eventual errors in the wave length scale of the photometer are of no consequence. An inexactitude of 5 nm at 304 nm leads to an error of the order of 1 % to 2 % in the photometer readings.

styrene to enable measurements to be made at relatively small depths. For the measurement of depth dose curves in a water phantom, the irradiation cells may be placed in a holder of polystyrene which causes no noticeable distortion of the radiation field. A proposed build up is shown in Fig. 3. It should be possible to irradiate up to 20 dosimeters at the same time so that a complete depth dose curve may be obtained during one irradiation.

Checking of the dosimeters against a known dose of ^{60}Co radiation. Many factors may affect the response of the ferrous sulphate dosimeter, such as impurities, the wall material of the irradiation cells, the storage of dosimeter solution in the cells, and the photometer calibration. The function of the dosimeter should therefore be tested. As the G value for ^{60}Co must be considered accurately determined since consistent results have been obtained with different measurement methods, this radiation quality seems preferable for such checking. The G value for ^{60}Co may be equalled to 15.6. An overall checking may be obtained by irradiating dosimeters to a known dose of ^{60}Co radiation and making a comparison with the dose calculated from the absorbance. Regular controls have been made for a long time in our laboratory. The difference between the dose calculated from the exposure measured with an ionization chamber at 5 cm depth in a water phantom and the dose measured with a ferrous sulphate dosimeter was about 1 %, giving a reproducibility of about 0.5 %. This deviation falls well within the limits of error ($\pm$ 2 %).

Intercomparisons between accelerator stations. Besides being a basic dosimeter for high energy electrons, the ferrous sulphate dosimeter may be used for intercomparisons between different laboratories (KRETSCHKO 1965, SAMIELEVICI & NAGL 1965 and WAMBERSIE et coll. 1965).

An intercomparison of dose measurements with high energy electrons was made in December 1964 for the betatrons in Helsinki and Umeå, and the results obtained are given in Table 2. A number of polystyrene irradiation cells were sent from Umeå to Helsinki where they were irradiated at different electron energies. Some were kept unirradiated and were irradiated when returned to Umeå, being then compared with dosimeters having been stored for the same period at Umeå. No differences were found between dosimeters that had been sent to and from Helsinki and dosimeters kept in Umeå. On the other hand, both these dosimeter groups gave an increased response of almost 6 %, as compared with dosimeters filled with fresh dosimeter solution immediately prior to irradiation. The higher response may be explained by the earlier mentioned storage effect appearing with cells of polystyrene when stored for about 2 days. After correction of the dose values with 3 %, the uncertainty

of 2 l is half filled with distilled water, and the contents of the test tube is poured into this flask Distilled water is added, some water being used for *rinsing the test tube to avoid loss of solution*, and the content adjusted to 2 l This solution is 10^{-3} M in ferric ions and 0 8 N in H_2SO_4, and gives an absorbance equal to 2 194 By suitable dilution of this solution with 0 8 N sulphuric acid (22 ml concentrated sulphuric acid per liter distilled water), prepared with the same water as the standard solution, calibration with different molalities can be carried out for checking the linearity of the photometer To ensure sufficient accuracy, only standardized transfer pipettes and standardized volumetric flasks should be used

The photometric measurement of a great number of dosimeters may be rather time consuming, and the same applies to the rinsing and filling of the dosimeter cells Instead of a pipette, the device shown in Fig 5 may be used Tube A is connected to a vacuum device, e g a water jet pump When flange B is pressed against the photometer cell, or the irradiation cell, liquid from tube D is filled into C By choosing suitable dimensions for tube D, the dosimeter solution may also be transferred directly from the irradiation cell to the photometer cell

Practical calibration procedures and determination of central ray doses At electron energies of more than 5 to 10 MeV the depth dose curve for the region of dose maximum is so flat that a calibration of the monitor of the accelerator may adequately be referred to the maximum dose along the central axis The choice of phantom material is not very critical for measurements at dose maximum As also the depth dose curves are to be measured, and as the temperature during irradiation is controlled more easily in a water phantom all monitor calibrations of the accelerator in Umeå refer to the dose in water

It is time consuming with the aid of the ferrous sulphate dosimeter to calibrate the monitor for all current field sizes and energies Experiments have shown that at fixed electron energy there is no measurable variation with field size in the ratios between the response of an ionization chamber and the ferrous sulphate dosimeter (SVENSSON & PETTERSSON, to be published) It is therefore possible to calibrate a suitable ionization chamber with the aid of the ferrous sulphate dosimeter only for one field at a given energy Other fields can thereafter be measured with ionization chambers of fixed calibration constant in rad/div for each energy

The dimensions of the phantom can be chosen in accordance with the recommendations in the ICRU Report 10d (1962) The radiation beam in many accelerators cannot be adjusted to point vertically downwards The phantom should therefore be equipped with a window, of e g 2 mm poly

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Le auteurs ont étudié expérimentalement l emploi d un dosimètre au sulfate ferreux comme dosimètre de base pour le rayonnement d électrons de haute énergie Ils décrivent ses qualités fondamentales et examinent les sources d erreur Ils décrivent une technique standard simple Ils rapportent brièvement le résultat de comparaisons dosimétriques entre différents laboratoires d accélérateurs effectuées au moyen de la dosimétrie par le sulfate ferreux

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ADENOID CYSTIC CARCINOMA OF THE PAROTID GLAND

by

CARL BLANCK, CARL MAGNUS ENEROTH, FOLKE JACOBSSON and PER Å JAKOBSSON

Adenoid cystic carcinoma and cylindroma are the usual designations for a type of tumour whose characteristic structure is reflected in these names The term cylindroma is used for several types of tumour, and therefore adenoid cystic carcinoma first adopted by SPIES (1930), is to be preferred

There is some uncertainty about the malignancy of adenoid cystic carcinoma This may be due to the absence of reliable investigations establishing correlations between its histologic features and clinical manifestations probably also to the rarity of the lesion and the wide margin between it and other tumour types in many classification systems

The object of the present investigation was to study the degree of malignancy of adenoid cystic carcinoma in a series of cases with long follow up studies

Material The investigation was based on the analysis of 1 678 histologically verified tumours of the parotid gland treated at Radiumhemmet from 1909

From Radiumhemmet (Acting Director Folke Jacobsson) the Departments of Otolaryngology (Director Carl Axel Hamberger) Pathology (Director Bo Thorell) and Radiopathology (Director Lars Santesson) Karolinska Sjukhuset Stockholm Sweden Submitted for publication 29 June 1966

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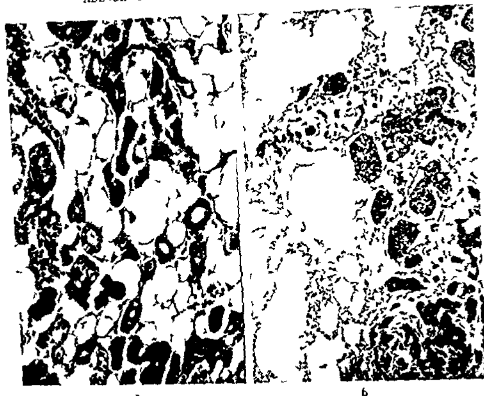


Fig 2 Adenoid cystic carcinoma (a) Tumour infiltrating adipose tissue H & E × 210 (b) Tumour growth in the form of thrombi in capillary vessels of the lung H & E × 78

patients lost to follow up or dying without evidence of malignancy No cases in the present series were lost to follow up Since long survival is common in this condition an extended follow up period is necessary for obtaining reliable prognostic figures The 35 patients in the group of adenoid cystic carcinoma were treated between 1921 and 1958 and all of them could be traced up to 1964

Pathologic findings

An analysis of the *gross* findings was precluded by the lack of sufficient data especially in the earlier cases

Microscopically, most of the tumours consisted of polycyclic cribrate or solid lobules of varying size often fairly well demarcated The compressed tissue around the tumour frequently resembled a fibrous capsule

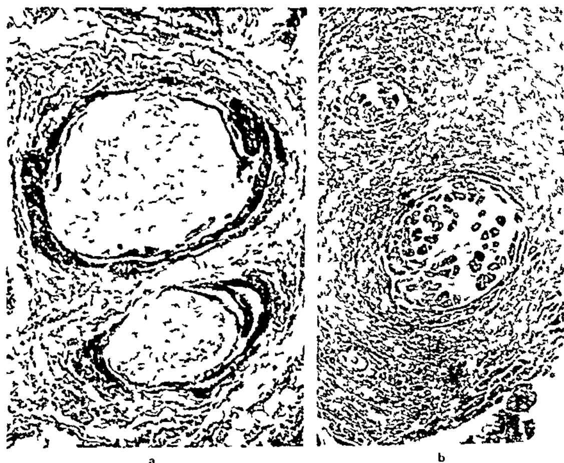


Fig 1 Adenoid cystic carcinoma a) Perineural tumour growth The tumour tissue is seen as dark sheaths encircling two medium sized nerves Van Gieson × 78 b) Massive tumour growth in and around a nerve H & E × 32

to 1958 During this period, a total of 1 928 cases of parotid tumours received treatment at the Institute, although 250 of them were not verified histologically

The prerequisites for a histologic re examination were present in 1 678 cases for which slides or paraffin blocks were archived, there were usually several blocks from each tumour The histologic review indicated that 299 were malignant, and 35 of these were adenoid cystic carcinomas Survival rate, presence of metastases and other clinical findings were studied The follow up periods were counted from the date of the first histologic verification of the tumour The cases had been followed up by regular annual examinations at Radiumhemmet, or by annual reports either from the outside doctor or the patient, in the latter instances, a check was performed if considered necessary

The survival rate is based on the determinate groups, which do not include

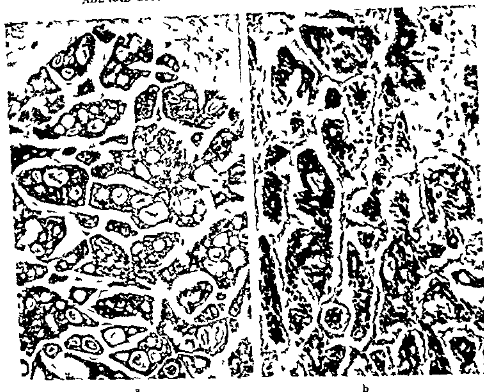


Fig 4 Most common tumour patterns in adenoid cystic carcinoma (cf fig 3) Cracking off artefacts around epithelial strands a) H & E × 78 b) The tumour pattern is slightly more solid than in (a) H & E × 210

layers of epithelium, others by one The majority of these structures had no real acinar arrangement however but were apparently empty spaces surrounded by solid epithelium (Figs 3 and 4) Where mucicarmine staining had been used the spaces were found to contain mucinous material, basophilic with haematoxylin and eosin staining

The cylindromatous structures the most characteristic features of these tumours could also give the impression of being glandular and cystic lumina especially with haematoxylin and eosin staining (Fig 3) These were areas where the stromal fibrous tissue had undergone hyaline change and in which the fibrous character was better brought out by van Gieson staining The extremely homogenous fibrous tissue with sparse nuclei either surrounded epithelial sheets or was enclosed by them

A few of the tumours had considerable areas of myxoid change (Figs 7b



Fig 3 Most common tumour patterns in adenoid cystic carcinoma (cf fig 4) a) H & E × 32 b) H & E × 78

The tumour is an adenocarcinoma but one with certain distinctive features The *most common type is illustrated* in Figs 3 and 4 The tumour lobules were composed of solid and more or less gland like, often cystic areas The cells of these lobules were generally small, with dark, rather hyperchromatic, isomorphic nuclei with a fairly amorphous structure The number of mitotic figures was usually low, mostly extremely low In eleven tumours, apparently the less differentiated ones, the cells were moderately polymorphous and the nuclei fairly large and vesicular The mitotic figures were numerous in eight tumours, that is to say, it was easy to find at least one mitotic figure in most of the high power fields (Fig 6a)

Within the epithelial *sheets of the lobules lay lumen like structures of various types*, often forming small cysts A few of these lumina had the appearance of true glands surrounded by radially arranged cells resembling those of a duct or a glandular acinus (Fig 6b) some of them were lined by two



Fig 4 M t common tumour patter s in ad noid cystic carcinoma (cf fig 3) Cracking-off rt f cts a ound ep thelial *strands a) H & E × 78 b)* The tumour pattern is slightly mo e solid than in (a) H & E × 210

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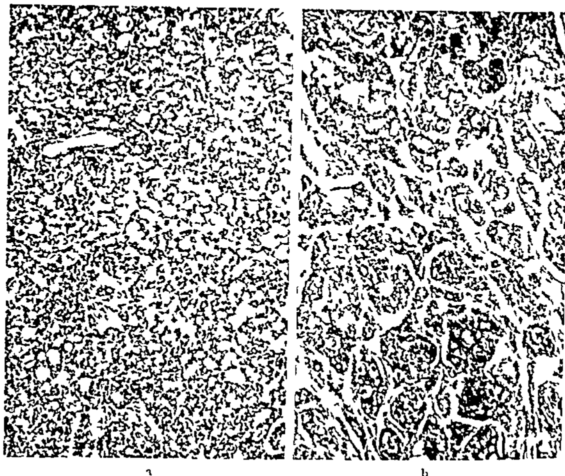


Fig 5 Adenoid cystic carcinoma Solid tumour pattern with much epithelium the adenoid cystic pattern being more distinct in (b) Both photomicrographs from same tumour H & E × 83

8b, and 9) which generally were clearly demarcated from the epithelial cells The boundary between the myxoid tissue and the epithelium was diffuse in only few cases, and then only in small areas The myxoid and hyaline tissue in the cylindromatous areas seemed to represent different stages of maturity of the mesenchyme Truly myxomatous areas were seen only in two tumours but even then gave the impression of retrogressive changes in the stroma rather than of being a true neoplastic component

Solid tumour tissue predominated in only an occasional case but cystic or non cystic lumina were present in every instance Twenty eight tumours displayed frank invasion of the salivary gland tissue, the surrounding soft tissues or nerves (Figs 1 and 2a), infiltration could not be established in the remaining seven tumour cases but in other respects these were indistinguishable from adenoid cystic carcinomas

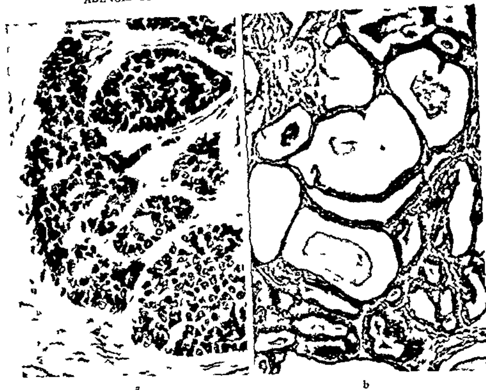


Fig 6 Adenoid cystic carcinoma a) Less common type with polymorphous cells some with mitotic figures H & E × 210 b) True gland formation H & E × 78

In some of the 28 cases with infiltrative growth, difficulty in establishing the presence of invasion was encountered because the tumours appeared to be of expansive rather than of invasive growth In these cases a study of the nerves in and near the tumour was often found to be of value Tumour infiltration of nerves was found to be characteristic of adenoid cystic carcinoma in 16 cases this took the form of perineural or intraneural growth and in 4 cases nerves were present within the tumour (Fig 1)

Intravascular growth was evident in none of the primary tumours but was present in metastatic tumours in the lungs in one case in which microscopic sections from autopsy specimens were available (Fig 2b) A peculiar structure was on the other hand, observed in 20 cases the connective tissue around the epithelial cords had cracked off leaving an empty cuff like space between the epithelium and the stroma This might be mistaken for growth in dilated capillaries but was almost certainly an artefact (Fig 4)

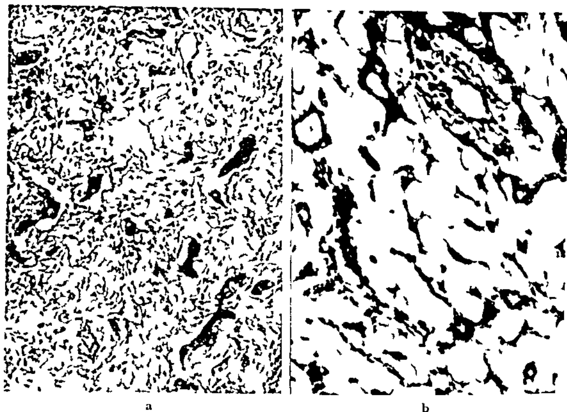


Fig 7 Adenoid cystic carcinoma a) The epithelial component is rather scarce and the fibrous — fibromatous — stroma tissue predominates strongly b) Hyalinized fibrous stroma is a predominant feature the epithelium occurs mostly as narrow solid strands a few glands are present Myxoid stromal change is seen at the top right corner For both photomicrographs H & E staining × 78

Clinical findings

Twenty of the 35 cases of adenoid cystic carcinoma occurred in women and fifteen in men The age of the patients when the tumour was first discovered ranged from 13 to 74 years (mean 45 6), and at the time of treatment, when the tumour was first confirmed by histologic examination, from 13 to 79 years (mean 49 3) The mean age in both instances was considerably lower for men than women when the tumour was first discovered 40 6 against 52 0 years and at the first treatment 44 8 against 55 3 years

Pain was recorded in fourteen and spontaneous facial paralysis in ten cases Otherwise, symptoms and signs other than palpable resistance in the parotid region were rarely recorded The mean interval between the first evidence of tumour and histologic verification was 3 7 years

Ten of the tumours were less than 3 cm fifteen were between 3 cm and 5 cm, and seven were larger than 5 cm in diameter in three cases the size was

not recorded The consistency, when mentioned was described as solid or hard The tumour was recorded as being firmly attached in nineteen and mobile in six of the 25 cases in which there were data on attachment and demarcation Thirteen tumours were completely attached at the first examination and at that time were considered inoperable The demarcation was indistinct in fourteen and well defined in eleven cases Dermal ulceration over the tumour was evident in one case Reliable data on such features as attachment consistency and demarcation on palpation were however too few to serve as reliable prognostic guides

Treatment data

Treatment was by no means uniform in the group In 29 cases the tumour was primary i e no treatment had been given previously, and in 6 cases treatment had been given earlier

Surgical treatment All the 35 cases underwent operations mostly conservative (Table 1) Minor operations constituted the largest group (31 cases) and included enucleation in one and extirpation in 17 cases In 13 cases sufficient data for classification of the nature of the operation could not be collected Only in four cases had fairly radical surgery been carried out, the effect of surgical treatment was therefore difficult to assess

Radiotherapy All but one case had received radiotherapy External irradiation before and after operation as well as intracavitary radium therapy at operation were used External radiotherapy was generally given by short distance techniques using either teleradium or ^{60}Co units with 6 to 7 cm distance between radiation source and skin (WALSTAM 1965) Intracavitary irradiation for 2 5 to 4 hours was generally administered by applying one to four 50 mg radium sources enclosed in a metal container of 10 mm diameter

Pre operative radiotherapy was usually applied over a circular field 6 cm in diameter 3 000 to 5 000 rad (2 mm tissue depth) being given over three to five treatment days occasionally a little longer Pre-operative irradiation by short distance technique was performed in 16 cases and in one case by 200 kV roentgen therapy Surgical measures usually extirpation followed 4 to 6 weeks later

Intracavitary radium therapy was given before suturing in 11 cases in nine of which pre operative irradiation had been employed as well

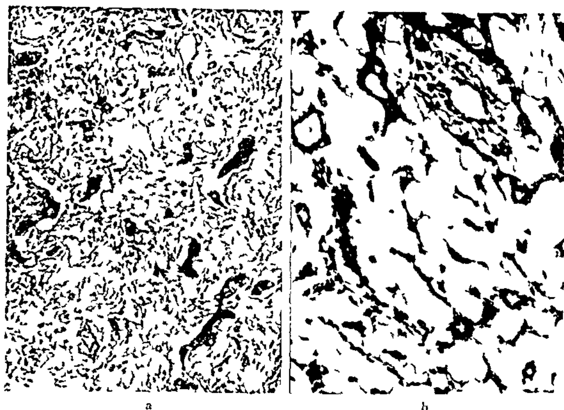


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appeared clinically in the course of 4 to 6 weeks after treatment — at the subsequent operation only small non palpable residues were present, the other five cases presented evidence of only moderate regression if any after the pre operative irradiation

Recurrence Local recurrence some time after the first operation occurred in 21 cases and 17 of these patients died from the disease Of the 14 patients with no local recurrence four died from tumour disease and five from inter current disease (see tabulation below)

	All cases	Death from tumour disease	Death from intercurrent disease
No recurrence	14	4	5
Recurrence	21	17	2

This confirms the grave implication of local recurrence Since it may be long before local recurrence appears a reliable assessment of the incidence calls for an extremely long follow up period In the group of 21 cases, the interval between treatment and local recurrence was as follows

11 years	2 cases
Between 6 and 10 years	8
1 and 5	8
Within a year	3

Metastases Metastases appeared in 15 cases in three of these they were detected on admission and in twelve during the follow up period The distribution was as follows

Metastases in the regional lymph nodes alone	3 cases
Distant metastases alone	8
Regional lymph node metastases and distant metastases	4

In all metastases in the regional lymph nodes were thus present in seven and distant metastases in twelve cases The sites of the distant metastases were as follows

Lungs	7 cases
Abdomen (not specified)	2
Kidney	1
Skeleton	3
Not specified	3

The most common site of the distant metastases was the lungs in some cases they were present at more than one site

Table 1

Adenoid cystic carcinoma type of operation at which the tumour was first verified histologically

	Primary	Secondary	Total
Minor operations (extirp)	25	6	31
Parotidectomy partial	1	—	1
» total	3	—	3
Total	29	6	35

Table 2

Adenoid cystic carcinoma interval between first symptom of primary tumour and appearance of metastases

Interval in years	Regional lymph node metastases	Distant metastases
0—5	2	3
6—10	3	2
11—15	2	4
> 15	0	3
Total	7	12

Postoperative radiotherapy was given in 17 cases A combination of three circular fields, 6 cm in diameter and 6 to 7 cm apart, was generally employed for external radiotherapy, with a dose of 4 500 to 5 000 rad to each field (maximum dose at 2 mm tissue depth) The estimated dose at 2 cm depth was generally of the order of 4 000 to 5 000 rad over three weeks

Radiosensitivity The radiosensitivity was considered to be high if a tumour that was easily palpable at first could hardly be felt 6 weeks after irradiation A high level of radiosensitivity was recorded in 17 of the 34 cases with primary tumours or recurrences in which radiotherapy had been given, in the other 17 cases irradiation did not result in much regression

It was possible to calculate the dose at different depths throughout the tumour mass fairly accurately in a smaller group of 9 primary tumours In these cases, pre operative therapy had been given by short distance technique to one circular field, 6 cm in diameter The dose maximum at a depth of 2 mm was calculated to be 3 500 to 5 000 rad given over 3 to 5 days The doses at the depths of 1 cm, 2 cm and 3 cm, were 2 700—4 300 2 100—3 700, and 1 700—3 500 rad, respectively In four of these nine cases the tumour dis

Table 3

Determinate survival rates in adenoid cystic carcinoma after the first histologic verification of tumour

Follow up in years	Number of cases	Death		Determinate survival rate		
		From carcinoma	Without sign of carcinoma	Number of cases	Survivals	
					Cases	%
5	35	9	2	33	24	73
10	31	16	5	26	10	39
15	23	15	4	19	4	21
20	19	14	3	16	2	13

The growth recurred with spontaneous facial paralysis in one case but not until 8 months later was a tumour palpable. Metastases occurred in six of the ten patients with spontaneous facial paralysis, distant in five of them and in the regional lymph nodes in one patient.

Histologic factors. An attempt was made to determine whether the micro-scopic appearances of the tumour provided any prognostic guide; the 35 cases of adenoid cystic carcinoma in the material was therefore studied with respect to the significance of peri- and/or intraneural growth. The observations made are recorded below.

	Number of cases	Death from tumour disease	Death from intercurrent disease
Present	16	13	2
Absent	19	8	6

Evidence of peri- and/or intraneural growth.

Thus thirteen of the 16 patients with such growth died from the condition as against only eight of the 19 patients without such growth.

The frequency of mitotic figures, the presence or absence of infiltrative growth, and the degree of polymorphism were also studied. The relation between these factors and death from the condition is shown in Table 4; it may be noted that death due to the condition occurred in seven of the eight cases with many mitotic figures.

Discussion

Pathology. As many of the tumours had been irradiated prior to operation, the histologic structure may have undergone alterations affecting the classi-

The regional cervical lymph node metastases were not evident until 5 to 15 years after the appearance of the first symptom in five of the seven cases involved (see Table 2) The interval between the first symptom and the discovery of the distant metastases was still longer over 10 years in seven of the twelve cases involved and over 15 years in three cases In five of the twelve cases they were found only at autopsy, and in three cases became evident only in the last year of life Only one patient with distant metastases survived more than 5 years

Prognosis The prognosis for adenoid cystic carcinoma of the parotid gland was evaluated chiefly from the survival time and the determinate survival rate during a follow up period ranging from 5 to 35 years The time elapsing from the first symptoms, to death (survival time) provides a measure of the malignancy of the tumour The intervals from the first symptom of primary tumour to death from adenoid cystic carcinoma of the parotid gland in the group of 21 cases were as follows

Interval in years	*0—5*	*6—10*	*11—15*	*16—20*	*>20*
Number of cases	3	5	9	3	1

It may be noted that, of the 21 patients who ultimately died from the condition, thirteen survived at least 10 years after the appearance of the primary tumour and four at least 15 years

The determinate survival rate provides a better basis for assessing the prognosis than does the survival time All the 35 cases were followed up for at least 5 years, of which 31 for at least 10 years, 23 for at least 15, and 19 for more than 20 years (Table 3) The determinate survival rate thus fell from 73 % for the cases followed up more than 5 years as compared to 13 % for the 20 year group

Clinical factors The consistency and demarcation of the growths were recorded in the analysis of the series to serve as guides in the evaluation of the prognosis, the data, however, often proved too unreliable for the purpose Also the recorded tumour size proved an unreliable basis for prognosis, though 6 of 7 patients with tumours more than 5 cm in diameter died, while only 15 of 25 patients with neoplasms less than 5 cm in size died from the tumour disease

Persistent spontaneous facial paralysis was present in 10 of the 35 patients within 10 years of the onset all these patients had died from the condition, 8 of them within 5 years (see tabulation below)

Survival time in years	*<1*	*1—3*	*3—5*	*5—10*	*>10*
Number of patients	1	2	5	2	0

a b

Fig 8 Adenoid cystic carcinomas with cylindromatous structure a) A fine reticular epithelial component is seen b) Myxoid change in the stroma the epithelial component is sharply delimited from the hyaline and *myxoid tissue* *H & E* staining a) × 87 b) × 79

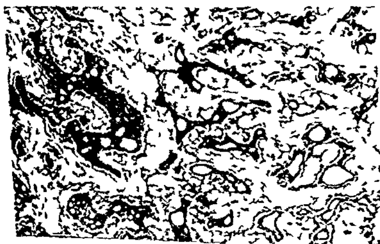


Fig 9 Same tumour as in fig 8b Area with myxoid change H & E × 225

Table 4

Tumour morphology and death from the tumour disease in adenoid cystic carcinoma

	All cases	Death from the tumour disease	Death from inter current disease
Mitotic figures			
Few	27	14	7
Many	8	7	0
Infiltrative growth			
Present	28	18	5
Absent or undecided	7	3	2
Polymorphism			
Slight	24	14	6
Moderate	11	7	1
Marked	0	0	0

fication Although the importance of this factor is difficult to assess it was not felt to constitute a major problem in the present study

Differential diagnosis The findings in the present series indicate that adenoid cystic carcinoma is a reasonably well defined tumour entity according to the criteria first laid down by Spies (1930) The greatest difficulty is to distinguish adenoid cystic carcinoma from malignant and benign mixed tumours Among the latter, it is mainly the purely fibro epithelial growths with more or less cyl indromatous structures that are the most troublesome (Foote & Frazell 1954, Thackray & Lucas 1960) There is less difficulty in distinguishing adenoid cystic carcinoma from mucus producing adenopapillary carcinoma and poorly differentiated solid types Muco epidermoid and acinic cell carcinomas are generally such well defined and characteristic tumour types that they should not be difficult to differentiate from adenoid cystic carcinoma

Benign mixed tumour of salivary gland origin At the first operation these lesions are histologically well encapsulated or clearly circumscribed They are usually distinguishable from adenoid cystic carcinoma by virtue of their myxomatous and chondromatous areas The remaining, fairly large group consists of purely fibro epithelial tumours of a type often described as cylindromatous The main point of difference between these and adenoid cystic carcinoma seems to be the more prominent glandular structure in the fibro epithelial mixed tumour, the glands being well formed and to a great extent lined by a two layered epithelium (Fig 10) The cells of the peripheral layer often possess the characteristics of myo epithelial cells There is no absolute differ

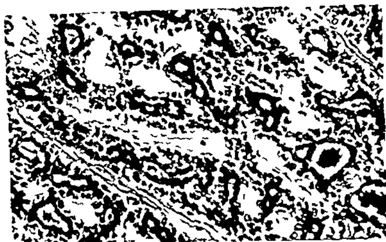


Fig 10 Mixed tumour of fibro-epithelial type Fairly regular structure of glands with glandular epithelium mostly in two more or less distinct layers H & E × 225

In 7 of the 35 cases no infiltrative growth was observed but it was none the less considered justified to classify these tumours as adenoid cystic carcinomas on the grounds of their general structure and even more so as three of the patients died of the tumour two of them with metastatic spread

The peculiar cracking-off artefact appears to be characteristic of adenoid cystic carcinoma as it was seen in 20 of the cases but rarely in the other tumour groups Although this trait could easily be misinterpreted as intra vascular tumour growth, this was precluded by the generally slow local spread and the often long interval before distant metastases were detected

Clinical findings Adenoid cystic carcinoma is a rare tumour, which according to KIRKLIN et coll (1951) constitutes 2 % to 5 % of the parotid neoplasms It occurred in 2 1 % of the parotid tumours in the present material and it represented 11 7 % of all the malignant parotid tumours The present com paratively large series has been treated and followed up at one hospital and the long follow up period provides a good opportunity for studying the be haviour of this neoplasm

Adenoid cystic carcinoma is characterized by a prolonged clinical course with a grave long term prognosis The determinate survival rate after the first histologic verification of the tumour was found to be 73 % for 5 years and only 13 % for 20 years The prolonged clinical course is reflected also in the late appearance of recurrences and metastatic spread

ence in this respect but only a difference in the extent to which the salivary duct structure is preserved

Myxomatous areas were present in two of the adenoid cystic carcinomas in the present material but these gave the impression of representing a degenerative change rather than a true component of the tumour itself, this is admittedly a subtle distinction THACKRAY & LUCAS (1960) pointed out that whereas the myxoid areas in adenoid cystic carcinoma are clearly demarcated from the epithelium, the border in the mixed tumour is ill defined We have gained the same impression

As THACKRAY & LUCAS stressed, the differential diagnosis between adenoid cystic carcinoma and a mixed tumour of salivary gland origin may certainly be difficult, and sometimes impossible, or it may be a matter of personal bias

Malignant mixed tumour of salivary gland origin Many of the observations made in the previous section also apply to malignant mixed tumours As the absolute criterion for this small group of tumours is evidence of infiltrative growth, their differentiation from adenoid cystic carcinoma was even more difficult than for the benign type The only safe criterion that could be adopted was the presence of myxomatous or chondromatous tissue in the malignant mixed tumours

Mucus producing adenopapillary carcinoma This is a purely fibro epithelial tumour with a marked tendency for papillary, often fine, growth, and more or less differentiated glandular structures There are no cylindromatous structures The epithelial cells are often larger and richer in cytoplasm, the nuclei are larger and more vesicular The mucus production varies greatly and the mucus is generally found inside the cell cytoplasm, whereas in adenoid cystic carcinoma it is usually present only in the glandular lumina

Poorly differentiated solid carcinoma There are a number of dark and small celled solid tumours that might be taken for poorly differentiated forms of adenoid cystic carcinoma The absence of glands, cystic structures, or cylindromatous areas, however distinguish them from adenoid cystic carcinoma (Fig 11)

Special histologic features The present series confirms that adenoid cystic carcinoma has a marked tendency for intra and perineural growth, as pointed out by, among others, QUATTLEBAUM et coll (1946), FOOTE & FRAZELL (1954), and MORAN et coll (1965) As it is often difficult to provide evidence of infiltrative growth in this type of tumour, a study of the relation of the tumour to the nerves may well prove of value

in spite of recurrence in order to ensure longer periods of freedom from clinical symptoms and to detain recurrences

The prognostic significance of distant metastases is hard to assess The figures given on p 188 provide a somewhat distorted picture because survival was reckoned from the time metastases were detected and this of course depends on the reliability of the individual follow up examination If however these figures are considered in the light of the interval between the first signs of primary tumour and the discovery of metastases (Table 2) a more reliable assessment of the prognostic significance is obtained In no less than seven of the twelve cases with distant metastases, were these latter not evident until at least 10 years after the appearance of the primary tumour

The radiosensitivity of adenoid cystic carcinoma is difficult to assess and estimates from a number of workers vary widely (AHLBOM 1935 BACLESSE 1946 FOOTE & FRAZELL 1954 BERDAL & MYLIUS 1954) If at 6 weeks after irradiation the tumour had regressed to such an extent that it could hardly be palpated, we considered it radiosensitive On this basis 17 tumours displayed considerable radiosensitivity It would seem however, that in operable cases or in those in which the tumour becomes operable after irradiation reliance should not be placed solely on radiotherapy even if the tumour has displayed radiosensitivity There was no case in this series in which the tumour could be said to have been banished for good by radiotherapy alone

Whether radiotherapy should be given before or after operation is difficult to decide on the basis of the present series

For recurrences which are often superficial irradiation should be used preferably with tele cobalt or electron radiation Such treatment given repeatedly, can retard the tumour growth and spare the patient much suffering especially from the severe constant pain that is one characteristic of adenoid cystic carcinoma Pain was present in 14 of the 35 cases included in the series (40 %) a figure that agrees with those (30 % to 50 %) reported by QUATTLEBAUM et coll (1946) KIRKLIN et coll (1951) RAUSCH (1959) BEAHRS et coll (1960) and GLASER (1962)

A marked improvement in the prognosis may well be achieved by centralizing the treatment of this rare and aggressive tumour to hospitals with facilities for suitable irradiation and radical operation

SUMMARY

A histologic re-examination and re-classification of a series of 1 678 parotid tumours revealed that 35 or 2 1 per cent were adenoid cystic carcinomas All the cases were followed up for at least 5 years and 19 of them for more than 20 years It is evident that the long term prognosis for this type of tumour is extremely poor and attention is drawn to the grave significance of spontaneous facial paralysis The pathology and treatment are discussed

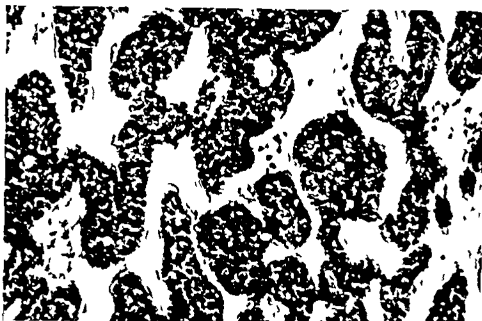


Fig 11 Poorly differentiated solid carcinoma No glandular or cystic structure the general tissue pattern *and the darkness of the epithelial component otherwise* bear a striking similarity to some of the less differentiated types of adenoid cystic carcinoma H & E × 225

A striking feature is the marked tendency to nerve involvement Microscopic evidence of intra and/or perineural growth implies a nearly hopeless prognosis as does also the clinical appearance of spontaneous facial paralysis The serious implications of the latter symptom have been illustrated by ENEROTH's study (1964) of a large tumour material, in which persistent spontaneous facial paralysis developed in 12 out of 515 cases of parotid tumours followed up for more than 5 years *All the patients died within* 5 years of the onset of this symptom, irrespective of the type of treatment *given, parotidectomy had been performed in nine of the twelve cases* This experience of the prognostic significance in cases of persistent spontaneous facial paralysis is borne out by the present study, paralysis developed in 29 % of the cases, a proportion that tallies well with the figures (25 % to 30 %) in earlier series, such as those reported by QUATTLEBAUM et coll and KIRKLIN et coll

The fairly high frequency of recurrence may well have been due in some measure to an unsatisfactory surgical operation With current surgical techniques and a more radical approach, the incidence of recurrence would be expected to be lower, according to results obtained in recent years Because of the prolonged clinical course it is important to persist with the treatment

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ZUSAMMENFASSUNG

Eine histologische Nachuntersuchung und Neuklassifizierung einer Serie von 1 678 Parotistumoren zeigte dass 35 Fälle (2 1 %) die characteristischen Zeichen eines adenoid zystischen Karzinoms aufwiesen Alle Patienten wurden mindestens 5 Jahre und 19 Patienten mehr als 20 Jahre nachuntersucht Es durfte klar sein dass die Prognose in derartigen Fallen äusserst schlecht ist auf die Bedeutung des Auftretens einer spontanen Facialislahmung wird hingewiesen Die Pathologie und therapeutischen Massnahmen werden besprochen

RÉSUMÉ

Un nouvel examen histologique et un reclassement de 1 678 tumeurs parotidiennes a montré que 35 cas soit 2 1 pour cent présentaient des structures caractéristiques de carcinome adénoide kystique Tous les malades ont été suivis au moins 5 ans et 19 de ces malades ont été suivis plus de 20 ans Il est évident que le prognostic de ce type de tumeur est extrême ment mauvais et les auteurs attirent l attention sur la signification grave de la paralysie faciale spontanée Ils étudient l anatomie pathologique et le traitement de ces tumeurs

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FROM THE GENERAL DEPARTMENT (DIRECTOR PROF ERIK POPPE) THE NORWEGIAN RADIUM HOSPITAL OSLO NORWAY

BONE SARCOMAS FOLLOWING EXTERNAL IRRADIATION

by

ÖYVIN P SOLHEIM

The basic information on bone tumour induction by irradiation in man is obtained from patients exposed to accidental irradiation and from radiotherapy The data from animal experiments and laboratory work are applicable to man only through this information which is still far from complete Less than one hundred malignant tumours following external irradiation of bone have been reported (CAHAN et coll 1948 PHILLIPS & SHELINE 1963 STEINER 1965) The majority of the tumours have arisen in bone where structure and metabolism were altered by disease at the time of irradiation The radiation dose was not always known Knowledge of this effect of radiation would naturally increase if all known cases were published

The Norwegian Radium Hospital admitted two cases of malignant bone tumours that occurred after irradiation of normal bone in the period 1932—1966

Case reports

Case 1 Male aged 40 was admitted following three attacks of haematuria treated at a local hospital Cystoscopy revealed papillomatous thickening of the bladder mucosa localized to

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Fig 1 Case 1 Normal bone structure before irradiation



Fig 2 Case 1 Osteosclerotic tumour of the right ilium and right side of sacrum 8 years after irradiation

the vesical base and not affecting the ureteric openings there were no signs of infiltration no biopsy was performed *Roentgenography of the pelvis indicated normal bone structure* (Fig 1)

The bladder was treated by irradiation cross fired from two anterior and two posterior fields Skin dose *3 500 R per field/46 days 175 kV filter 1 mm FSD 50 cm* angulation 25 degrees for the anterior fields 35 degrees for the posterior fields Later calculation revealed that the dose to the bone in question had been 2 800 $\pm$ 700 R/46 days



Fig 3 Case 2 Chronic skin changes following roentgen irradiation 8 years previously The three fields of treatment have been indicated by pencil

The patient remained well for eight years Then he developed increasing pain in the right side of the pelvis He was readmitted six months later with a palpable tumour in the right lumbo-sacral region The lower extremity was partly paretic and slightly edematous Roentgenograms revealed a large osteosclerotic tumour of the right ilium and the right side of the sacrum (Fig 2) no visible changes on the left side Biopsy from the tumour disclosed an osteochondrosarcoma Multiple lung metastases were present Cystoscopy and proctoscopy were negative The patient was discharged without treatment and died four weeks later

Case 2 Male who at the age of 47 had a tumour in the left inguinal region this was removed and the area treated by irradiation Inguinal lymph node dissection was carried out a few months later in the local hospital Histologic examination revealed a poorly differentiated tumour probably a reticulosarcoma The patient was treated postoperatively with large doses of conventional roentgen radiation to three crossing fields A total skin dose of 7 500 R was given to a left inguinal field 5 600 R to the left hip and 5 600 to the left side of the sacrum The dose to the bone is assumed to have been 4 300 $\pm$ 500 R over several months Roentgenograms of the pelvis were negative for three years but the patient later developed edema of the left lower extremity and slight flexure of the hip

Eight years following the irradiation the patient developed increasing pain in the left hip and he was admitted to our hospital There were marked skin changes in the fields treated (Fig 3) edema of the left leg and a 20-degree flexion of the hip Roentgenograms disclosed osteolytic and osteosclerotic areas in the left wing of the ilium similar changes were present in the trochanteric region (Fig 4a) and were interpreted as radiation damage with probable malignant degeneration Angiography did not confirm the diagnosis (Fig 4b) but biopsy of a specimen from the ilium revealed osteosarcoma (NRH 4904/59) The patient was discharged and died nine months later having received palliative radiation treatment in the local hospital Autopsy confirmed the diagnosis of osteosarcoma

Discussion

The incidence of many kinds of tumours including osteogenic sarcomas is increased in previously irradiated tissue PHILLIPS & SHELINE reported two

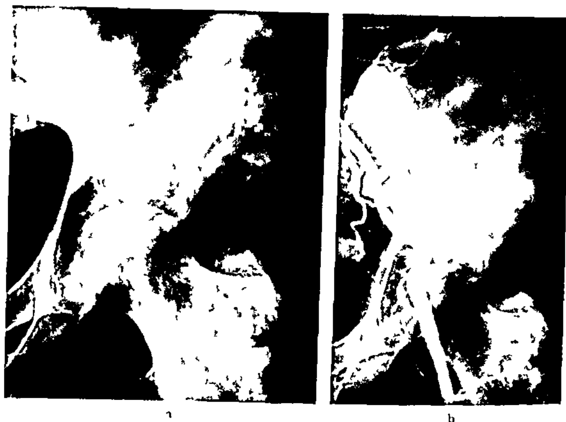


Fig. 4. Case 2. a) Osteosclerosis and osteolysis of the left wing of the ilium and lateral part of the trochanteric region 8 years after irradiation. b) In the angiogram no abnormal vessels in the region of pathologically changed bone, no deposits of contrast medium, nor any rapid filling of veins. (Biopsy revealed osteosarcoma with irradiation changes.)

radio induced osteogenic sarcomas among 2 300 patients living more than five years after irradiation. More than 30 000 patients have been treated in our centre since 1932, one of these developed an osteogenic sarcoma in bone that was unaltered by disease at the time of irradiation. This low frequency is very different from the results in animal experiments where the tumour incidence is 20% or more.

The age of the patients now reported upon, 40 and 42 years, respectively, the tumour sites in ilium and sacrum, the latency period of 8 years in both, and the radiation dose, 2 800±700 R/46 days and 4 300±500 R over several months, all fall within the previously reported wide range.

There has been no report on radiation induced malignant bone tumours following roentgen irradiation of normal bone in man when the bone dose has been less than 3 000 R.

SUMMARY

Two cases of malignant bone tumours following roentgen therapy diagnosed by clinical roentgenologic and histologic investigations are reported

ZUSAMMENFASSUNG

Es wird uber zwei Falle mit bosartigen Knochentumoren nach Rontgentherapie berichtet Die Diagnose konnte klinisch rontgenologisch und histologisch bestatigt werden

RÉSUMÉ

Présentation de deux cas de tumeur maligne des os apres roentgenthérapie avec leur diagnostic clinique radiologique et histologique

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TETRACYCLINE FLUORESCENCE AND ENZYME HISTOCHEMISTRY ON EARLY RADIATION DAMAGE IN MOUSE KIDNEY

by

J RAEKALLIO and I LINDGREN

Radiation damage occurs histologically in partial or complete degeneration of the cells The histologic evidence of cell damage is, however, a relatively late phenomenon On the other hand, by the methods of enzyme histochemistry it is possible to detect and localize early functional changes This has been shown in connection with wound healing where a decrease in enzyme activity reveals the necrobiosis in the immediate vicinity of the wound edge as early as one hour after the mechanical injury (RAEKALLIO 1960, 1965) Furthermore, tetracyclines have an affinity to necrobiotic sites This is demonstrable before the imminent necrosis becomes histologically recognizable (KOVACZ, CARROLL & TAPP 1964, LINDGREN & RAEKALLIO 1966) An attempt was therefore made in the present work to demonstrate the radiation damage in mouse kidney by the methods of tetracycline fluorescence and enzyme histochemistry

Material and Methods Male white mice weighing 20 to 25 g, were used All experimental animals received 100 mg per kg bodyweight intramuscular

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F g 1 Fluorogram of a control kidney that had not been irradiated There are traces only of tetracycline fluorescence

terramycin (Pfizer) by daily injections for three days before the operation and when still living also postoperatively The anaesthesia was initiated with 0 1 to 0 2 ml sodium amytal 1 % intraperitoneally and continued with ether The left kidney was completely mobilized from its bed in order that it should be accessible to strictly local irradiation it remained attached by its pedicle only where the circulation continued The other kidney serving as a control remained intra abdominal The mobilized left kidney was placed on a 5 mm lead sheet to avoid *the effects* of wholebody irradiation The radiation was delivered by a Machlett roentgen tube with a tungsten target and a 0 5 mm beryllium window the tube was run at 50 kV Two doses were used 1 000 R or 3 000 R

The animals were killed 1 2 4 8 and 16 hours or 1 7 and 14 days after irradiation The kidneys were removed immediately and frozen in isopentane maintained at — 70 C with a mixture of acetone and dry ice

Tetracyclines were observed in untreated cryostat cut sections by fluorescence microscopy with an Osram high vapour HBO 200 mercury lamp and B 12 (4 mm) filters The wavelength of the transmitted light was 550 Å

Adjacent sections of the *frozen* specimens cut in a cryostat at 16 μ were studied histochemically Cytochrome oxidase activity was demonstrated in

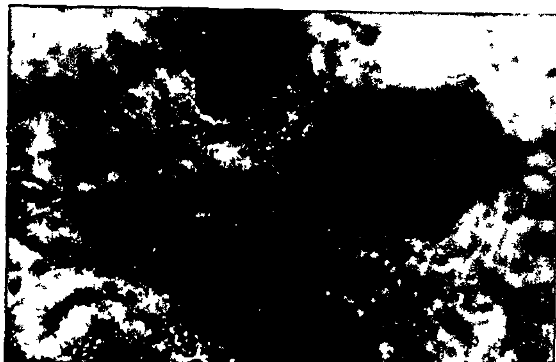


Fig. 2. Fluorogram of an irradiated kidney 4 hrs after 3 000 R with numerous bright spots due to tetracycline deposits.

the fresh frozen sections by the BURSTONE method (1959), and aminopeptidase activity by the technique of NACHLAS et coll. (1957). The incubation times were 30 to 15 minutes, respectively. Alternate frozen sections were fixed at + 4° C in neutral 10 % formalin. The activity of acid phosphatase was demonstrated by the standard coupling azo dye technique — incubation time 60 minutes (PEARSE 1960). In addition, some of the fixed sections were investigated histologically by the Van Gieson method.

The sections of the irradiated kidney were compared to those of the control kidney of the same animal.

Results

There was very little tetracycline fluorescence in the control kidneys (Fig. 1) and that observed was confined to the tubular lumina and to the surrounding parts of the tubule cells. The dose of 1 000 R caused no demonstrable changes. The first increase in tetracycline fluorescence was noted two hours after the exposure in the kidneys irradiated with 3 000 R. This was especially evident

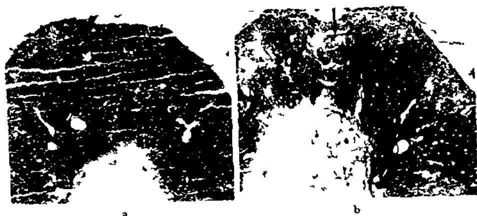


Fig 3 a) Aminopeptidase activity of a control kidney (no irradiation) b) Aminopeptidase activity of an irradiated kidney 24 hrs after 3 000 R Large cortical areas with little or no enzyme activity the arrow indicates the radiation beam

in the part of the kidney that had been nearest to the radiation source There was an initial increase in tetracycline fluorescence in the tubule cells This became more apparent four hours after the irradiation (Fig 2) and still more striking later There was no fluorescence in the glomeruli nor in the blood vessels The increased tetracycline fluorescence of the tubule cell was demonstrable even 14 days after irradiation

Distinct aminopeptidase and acid phosphatase activity was observed histochemically in the tubuli and glomeruli of the control kidneys(Fig 3a) There was no cytochrome oxidase activity in the glomeruli but a definite cytochrome reaction in the tubule cells (Fig 4a) The dose of 1 000 R caused no visible histochemical changes during the whole experimental period but four hours after the irradiation dose of 3 000 R the first patchy decrease in aminopeptidase and cytochrome oxidase activity could be observed This was most conspicuous in the region of the kidney that had been closest to the radiation source Eight hours after the irradiation with 3 000 R the decrease in aminopeptidase and cytochrome oxidase activity became still more definite and some decrease in the acid phosphatase activity was also evident Later on large cortical areas with little or no enzyme activity appeared (Figs 3b and 4b) The disappearance of enzyme activity was most conspicuous in the outer cortex of the irradiated kidney Some residual activity persisted in the inner cortex

The first signs of necrosis karyolysis and karyorrhexis were histologically demonstrable 24 hours after the irradiation dose of 3 000 R The patchy necrosis became more apparent 7 and 14 days after irradiation



Fig. 4. a) Cytochrome oxidase activity of a control kidney. b) Cytochrome oxidase activity of an irradiated kidney 16 hrs after 3 000 R, with cortical decrease in enzyme activity; the arrow indicates the radiation beam.

Conclusion

It was accepted as a working hypothesis that enzyme histochemistry and tetracycline fluorescence will reveal radiation damage before it becomes demonstrable histologically. This, in fact, was proved, since a decrease in enzyme activity was present as early as four hours after irradiation, and an increase in tetracycline fluorescence at the same time or still earlier. Both of the changes were thus demonstrable long before histologic evidence of cell damage became apparent. The early affinity of tetracyclines to necrobiotic sites has previously been demonstrated by Kovacs et coll. (1964) and by Lindgren & Raekallio (1966). The decrease in enzyme activity seems to be a general early sign of necrobiosis. This has previously been shown in mechanical trauma (wound healing) (Raekallio 1960, 1961, 1965), or in ischemia (experimental myocardial infarction) (Bajusz & Jasmin 1964, Jaaskelainen 1966).

The radiation used was relatively soft, as indicated by the low voltage (50 kV). Thus, most of the radiation was absorbed by that part of the kidney that was closest to the radiation source. This could be demonstrated by the most conspicuous loss of enzyme activity in the outer renal cortex (Figs 3b and 4b).

Bacq & Alexander (1961), in a review of the biochemical and biophysical work on radiation cell damage, suggested that radiation could disrupt phospholipid membranes of lysosomes, releasing hydrolytic enzymes, such as acid phosphatase. This is quite possible. However, it cannot be the only mechanism producing the early enzyme changes observed in the present investigation.

Cytochrome oxidase is not a lysosomal but a mitochondrial enzyme, and there is lack of proof that aminopeptidase is a lysosomal enzyme (GREENSPAN et coll 1964) There could consequently be disruption of some other subcellular particles as well In addition a decrease in enzyme activity could simply indicate an imminent decrease in metabolic function of the damaged cells

Acknowledgements

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SUMMARY

Irradiated mouse kidneys were studied by tetracycline fluorescence and enzyme histochemistry to investigate early radiation damage There was an increase in the tetracycline fluorescence of tubule cells a early as 2—4 hrs after irradiation Aminopeptidase and cytochrome oxidase activity decreased at 4 hrs and acid phosphatase at 8 hrs At 24 hrs there were large cortical areas showing little or no enzyme activity The changes in enzyme activity and in tetracycline fluorescence revealed early signs of imminent necrosis long before there was histological evidence of cell damage

ZUSAMMENFASSUNG

Um fruhzeitige Bestrahlungsschaden zu studieren wurden Nieren von Mausen mittels Tetracyclinfluoreszenz und Histochemie der Enzyme untersucht Eine Zunahme des Tetracyclinfluoreszenzes konnte in den Tubuluszellen bereits nach 2 bis 4 Stunden nach der Bestrahlung festgestellt werden Die Aminopeptidase und Cytochromoxydase Aktivitat nahmen nach 4 Stunden ab und die saure Phosphotase nach 8 Stunden Nach 24 Stunden zeigten grosse Nierenrindengebiete geringe oder keine Enzymaktivitat Mit diesen Methoden konnte eine beginnende Nekrobiose festgestellt werden lange bevor histologische Zellschadigungen erkennbar waren

RÉSUMÉ

Les effets précoces de l irradiation localisée a un rein ont été étudiés chez la souris par la fluorescence a la tétracycline et par l histochimie des enzymes La fluorescence à la tétracycline dans les cellules des tubes augmentait dès la 2 ou 4 heure après l irradiation L activité de l amnopeptidase et de la cytochrome oxydase diminuait a la 4 heure et celle de la phosphatase acide à la 8 heure À la 24 heure de larges aires corticales montraient une activité enzymatique faible ou nulle Les modifications de l activité enzymatique et de la fluorescence à la tétracycline révèlent des signes précoces de nécrose imminente longtemps avant qu il ait des signes histologiques de lésion cellulaire

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EFFECTS OF RADIOSTRONTIUM AND ROENTGEN RAYS ON GERM CELLS OF MALE MICE

by

B HENRICSON and A NILSSON

The effects of ^{90}Sr and roentgen rays on germ cells of male mice were compared in an earlier work (HENRICSSON & NILSSON 1965) Only one dose of strontium (0 7 μCi/g bodyweight intravenously) was used, and the killing effect of this dose was comparable to irradiation with 12 to 25 R

The present study deals with different doses of ^{90}Sr and the time between treatment and evaluation has been extended from 3 or 5 days to 10 days

Materials and Methods Inbred male CBA mice 75 days old were injected intravenously with ^{90}Sr or treated with roentgen rays The roentgen equipment was a Muller MG 300 apparatus operated at 260 kV 10 mA focal distance 40 cm inherent filtration 4 mm Al additional filter 0 5 mm Cu giving a dose rate of 85 R/min Total body irradiation was applied Groups of 5 mice were exposed to 12 25 50 or 100 R roentgen rays In the case of ^{90}Sr each group of 5 mice was given 0 1 0 3 0 5 0 7 or 1 4 μCi/g bodyweight As an extra check of the 0 7 μCi dose this group included 8 animals

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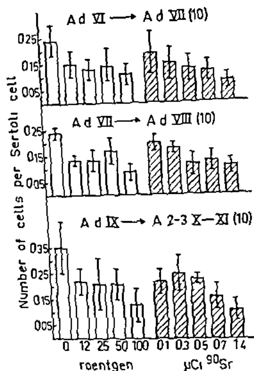


Fig 1 Mean number and 95 % confidence interval of spermatogonia type A per Sertoli cell per tubular cross section

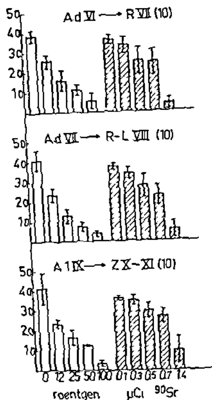


Fig 2 Mean number and 95 % confidence interval of primary spermatocytes per Sertoli cell per tubular cross section

Symbols to the left of the arrows indicate cell type and tubular stage irradiated, symbols to the right of the arrows indicate those scored (10) indicates the number of days between treatment and scoring Roman figures indicate tubular stages For further symbols cf Table

The results with the different doses of roentgen and ⁹⁰Sr are given in Figs 1—2 Each staple represents the *mean* number of cells per Sertoli cell for five (in the case of 0 7 µCi ⁹⁰Sr/g bodyweight for eight) mice The 95 % confidence interval is also given

Discussion

The cell killing effect of roentgen rays obtained in the present investigation corresponds with earlier results (HENRICSON & NILSSON 1965) Thus the cells which have to pass several periods of DNA synthesis show enhanced *sensitivity*

Table

Cell types and tubular stages involved in the investigation

Irradiation		Critical stages to pass	Time between treatment and scoring	Scoring	
Cell type	Stage			Cell type	Stage
A d	VI	VIII	10 days	A d	VII
A d	VII	VIII	10 days	A d	VIII
A d	IX	VIII	10 days	A 2—3	X XI
A d	IX	VIII X XII II III VI	10 days	R	VII
A d	VII	VIII X XII II III VI	10 days	R I	VIII
A 1	IX	X XII II III VI	10 days	Z	X XI

A d = Dormant spermatogonia type A A 1 = first generation spermatogonia type A A 2—3 = second third generation spermatogonia type A R = resting primary spermatocytes I = leptotene primary spermatocytes and Z = zygotene primary spermatocytes

The animals were killed ten days after treatment The left testicle was removed and immediately fixed in Stieve s fluid After embedding, the testicle was sectioned at 4 μ and stained according to Hotchkiss' PAS method Five mice were used as controls and their testicles were prepared at the age of 85 days

Circular cross sections of 10 tubules were selected at random from the stages VII, VIII and X-XI *of the cycle of the seminiferous* epithelium (OAKBERG 1956) Sertoli cells, spermatogonia and primary spermatocytes (resting leptotene and zygotene) were counted The number of germ cells per cross section was referred to the number of Sertoli cells present

Results

In this investigation, all cells were scored ten days after treatment They were thus irradiated as A spermatogonias of the dormant type (A d) in all cases, with the exception of the cells counted as zygotene nuclei in stage X XI When irradiated, these cells were A spermatogonias of the first generation (A 1) The relationship between the cell types irradiated and the cell types scored, and also the critical stages they have to pass between treatment and scoring, are indicated in a Table For A spermatogonias and intermediate spermato gonias these stages correspond to the time of DNA synthesis (late interphase and early prophase), and for the B type to the pre DNA synthesis interval (anaphase and telophase) according to MONESI 1962

von 0 7 μCi/g Korpergewicht von ^{90}Sr entspricht etwa 12 R Falls diese Zellteilungsphasen nicht passiert werden mussen so ist die Empfindlichkeit nicht so hoch und der Effekt zwischen 12 bis 50 R scheint gleich zu sein In diesem Falle zeigt der Effekt von ^{90}Sr zwischen 0 1 und 1 4 μCi/g ein geradlinigeres Muster

RÉSUME

Chez les souris de souche CBA l effet léthal des rayons roentgen sur les spermatogonies de type A est relativement important (LD_{50} = 12 à 25 R) si ces cellules doivent subir plusieurs divisions spermatogoniques comprenant le typ B de spermatogonies avant scoring L administration de 0 7 μCi/g de poids corporel de ^{90}Sr correspond à environ 12 R Si ces cellules n ont pas à subir ces phases de divisions leur sensibilité est moindre et l effet de l irradiation semble être le même entre 12 et 50 R Dans ce cas l effet de ^{90}Sr paraît varier de façon plus linéaire en fonction de la dose entre 0 1 et 1 4 μCi/g

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with increasing dose (Fig 2) In our earlier investigation it was apparent that cells irradiated as A-spermatogonia of the third to fourth generations, or as intermediary- or B types, were extremely sensitive It is obvious from Fig 2 that roentgen irradiated cells which have to go through these phases will be profoundly damaged even if they were treated as dormant A spermatogonias Consequently, their ability to recover seems to be strongly disturbed In the ^{90}Sr groups, on the other hand, this very high cell killing effect is reached only with a dose of 1 4 μCi/g bodyweight This dose corresponds approximately to 100 R roentgen irradiation The doses between 0 1 to 0 7 μCi ^{90}Sr show little mutual difference and correspond to a roentgen dose of zero to 12 R

A spermatogonias are considered by OAKBERG 1957 and MONESI 1962 to be of heterogeneous sensitivity, which is also in agreement with the present findings Thus, the sensitivity of A spermatogonias which have had to pass only one stage of DNA-synthesis show a marked resistance (Fig 1) in comparison with cells which have gone through several DNA periods The effect of roentgen rays is about the same for doses between 12 to 50 R, and only at 100 R is an increase seen In the ^{90}Sr series there is not much difference between the 0 1 to 0 7 μCi/groups These doses correspond to about 12 to 50 R roentgen rays, and the 1 4 μCi group to approximately 100 R

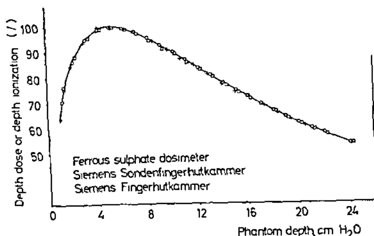
Concerning the dormant type of A spermatogonias our earlier paper gave some argument for a theory that irradiation with roentgen rays, given very close to a period of DNA synthesis should be especially critical If, on the other hand, the cells are exposed some time before DNA synthesis starts the cells may be expected to have recovered to some extent In the present experiment there was a slight tendency towards a similar effect The cells irradiated at stage VII (closest to the DNA synthesis at stage VIII) seem to have been slightly more reduced in number in comparison with those irradiated at stage VI or stage IX (Fig 1)

SUMMARY

The lethal effect of roentgen rays on spermatogonia A in inbred CBA mice is relatively high (LD_{50} = 12 to 25 R) if the cells have to pass several spermatogonial divisions including type B spermatogonia before scoring The effect of the administration of 0 7 μCi/g bodyweight of ^{90}Sr corresponds to about 12 R When the cells do not have to pass these division phases the effects in the range between 12 to 50 R seem to be similar and the sensitivity is lower while the effects of ^{90}Sr between 0 1 and 1 4 μCi/g bodyweight show a more linear pattern

ZUSAMMENFASSUNG

Der Lethaleffekt der Rontgenbestrahlung auf die Typ A Spermatogonien bei CBA Mausen wird verhaltnismassig gross (LD_{50} = 12 bis 25 R) wenn die Zellen mehrere Spermatogenese einschliesslich Typ B Spermatogenese bevor scoring passieren mussen Die Verabreichung



Comparison between relative depth dose and depth ionization values obtained along the central ray in a water phantom exposed to 34 MV roentgen radiation. The effective measurement point of the thimble chambers was assumed to be in front of the centre at a distance of three fourths of the radius of the air cavity. FSD 100, field 10 cm × 10 cm.

Method. The radiation source was a Brown Boveri betatron, the Asklepitron. The maximum photon energy was measured by means of threshold determinations of photon/neutron interactions. During calibration an external monitor was used, the linearity and reproducibility of which had been found satisfactory for the investigation.

The ferrous sulphate solution was kept in small polystyrene irradiation cells during the determination of the depth dose curves. The dosimeters were placed in a stand along the central axis inside a water phantom, 25 × 25 × 30 cm in size, and the irradiations were performed with phantom and dosimeters kept at a temperature of 25° C. Separate measurements had indicated that the ferrous sulphate solution, the dosimeter cells, and the stand had no influence on the radiation field to be measured.

The G value was assumed to be 15.5 $(100\ eV)^{-1}$ and was estimated from calorimetric G value determinations with a 0.8 N dosimeter solution at 15—30 MeV electron radiation and ⁶⁰Co gamma radiation (PETTERSSON, to be published). Further details on the technique of dose measurements with ferrous sulphate dosimeters will be given in a separate paper (PETTERSSON & HETTINGER 1967).

The thimble chambers were placed in well defined positions along the central ray for the determination of the depth ionization curves. The effective meas

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CALIBRATION OF THIMBLE CHAMBERS IN A 34 MV ROENTGEN BEAM

by

G HETTINGER, C PETTERSSON and H SVENSSON

High energy roentgen radiation from accelerators has during the past decade been used for therapy to an ever increasing extent but no standard methods have as yet been recommended for the determination of the dose absorbed at these photon energies Since no international recommendations exist, treatment doses in the clinics are often based on different units, and under such conditions intercomparisons between different therapeutic methods and results will suffer

This paper deals with the absorbed dose calibration of some commercial thimble chambers against ferrous sulphate dosimeters for 34 MV roentgen radiation The calibrations were carried out at different depths along the central ray in a water phantom The calibration factor obtained for each thimble chamber, in rad unit (water) per scale division, is compared with the exposure calibration for ^{60}Co gamma radiation in a manner similar to that used by the Hospital Physicists' Association (see ref 'Code of practice for the dosimetry of 2 to 8 MV X ray and caesium 137 and cobalt 60 γ ray beams 1964)

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calibrated at the Swedish National Institute of Radiation Protection and the calibrations should be correct within 2 % It may be seen from the Table that the ratio between the calibration factors in columns I and II as given in the third column is practically the same for all the four chambers studied

The absorbed dose in water, irradiated by 34 MV roentgen rays, may consequently be written $D = 0.92 \times k_{C_o} \times I$ (rad) where D is the absorbed dose in water at the effective measurement point of the chamber, k_{Co} the exposure calibration with build up cap for ^{60}Co gamma radiation, and I the instrument reading when the chamber without build up cap is irradiated in water by 34 MV roentgen rays

Acknowledgement

This work was supported by grants from the Swedish Cancer Society

SUMMARY

Ionization chambers were calibrated against ferrous sulphate dosimeters in a water phantom exposed to 34 MV roentgen radiation and the values obtained were practically the same at all depths The ratio between the dose calibration for 34 MV roentgen rays and the exposure factor for ^{60}Co gamma radiation was the same with all the four chambers used

ZUSAMMENFASSUNG

Kalibrierung von Ionisationskammern mittels Eisensulfat Dosismetern bei Rontgenbestrahlung von einem Wasserphantom mit 34 MV wurde vorgenommen bei verschiedenen Tiefen wurden etwa dieselbe Messwerte erhalten Die Verhaltniszahl Dosis Kalibrierung fur 34 MV Rontgen versus Exponierungsfaktor fur Co Gammastrahlen war dieselbe mit den vier Kammern

RÉSUMÉ

Des chambres d ionisation étalonnées par rapport à des dosimètres a sulfate ferreux dans un fantôme d eau exposé au rayonnement roentgen de 34 MV gardent pratiquement le même étalonnage à toutes les profondeurs Le rapport entre l étalonnage de dose au rayonnement roentgen de 34 MV et le facteur d exposition aux rayonnements gamma du ^{60}Co est le même pour les quatre chambres étudiées

Table

Dose calibration of four thimble chambers against ferrous sulphate dosimeters in a water phantom irradiated with 34 MV roentgen rays. — The ratio between the dose calibration at 34 MV and the exposure calibration of ^{60}Co gamma rays is nearly the same for all four chambers studied

Chambers used	I rad/scale division H_2O 34 MV roentgen rays	II R/scale division ^{60}Co gamma rays	I/II
Siemens Sondenfingerhutkammer (E 28 RO9 512 with E 3T7 1335)	10.32	11.27	0.917
Siemens Fingerhutkammer (E 30 R1 757 with E 3T7 1335)	1.031	1.109	0.918
Philips Intracavity chamber (G 394 028 with G 277007)	1.061	1.161	0.913
Baldwin Farmer Substandard M2 (54 7608 with 547615)	0.967	1.055	0.916

urement point of a thimble chamber, according to an earlier investigation (HETTINGER et coll. 1967), has been found to be in front of the centre at a distance of three fourths of the radius of the air cavity.

Results

A comparison between the relative depth dose and relative depth ionization values is presented in the diagram accompanying this paper. The ionization was measured with two different thimble chambers, a Siemens Sondenfinger hutkammer, with a radius of 3 mm, and a Siemens Fingerhutkammer with a radius of 8 mm. The good agreement between the values obtained indicates that the dose calibration factors for these two chambers will remain the same at all depths. This, of course, will be true only if the effective measurement point of the chamber is selected as mentioned above. Measurements off the beam axis resulted in equal calibration factors. Results similar to those represented in our diagram were obtained for other thimble chambers as well.

The results from a calibration of four different thimble chambers at dose maximum are given in the Table. The calibration factors are the mean values of at least two independent measurements, and, according to our diagram, they are valid for depths between 1 cm and 24 cm.

The absorbed dose in water per electrometer scale division is recorded in the first column, and, for comparison, the exposure calibration with a build up cap at ^{60}Co gamma radiation in the second column. The chambers were

calibrated at the Swedish National Institute of Radiation Protection and the calibrations should be correct within 2 % It may be seen from the Table that the ratio between the calibration factors in columns I and II as given in the third column is practically the same for all the four chambers studied

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FROM LABORATOIRE DE RECHERCHES POUR LA PROTECTION DES POPULATIONS CIVILES LABORATOIRES DE RADIOBIOLOGIE UNIVERSITE DE LIEGE BELGIUM

PREMISES FOR THE NEW 2 000 CURIE CESIUM 137 RADIATION UNIT

by

G NOLET J GILLET and Z M BACQ

Research in radiobiology during the last ten years has necessitated that more information be obtained on the effect of protraction Radiophysiologists biochemists and geneticists are all interested in low dose rates, and micro biologists and radiochemists are interested in high dose rates for irradiation of small samples Many problems of health physics cannot be handled unless a specifically designed room is available for irradiation at various dose levels of animals as well as plants The authors feel that with the installation to be described these requirements have been answered and that the reporting of our experience may be of help to others who wish to build their own special irradiation laboratory

The *entire irradiation room* is in concrete (Fig 1) It is cylindric in shape with a diameter of 7 meter and it has a height of 2 meter (inner dimensions) The room is fitted with wall racks central shelves and small tables suspended from the ceiling enabling the irradiation objects to be placed at varying distan ces from the source from 3 5 meter to 20 centimeter A door that can be locked

This work was sponsored by NATO contract No 161 Submitted for publication 9 June 1966

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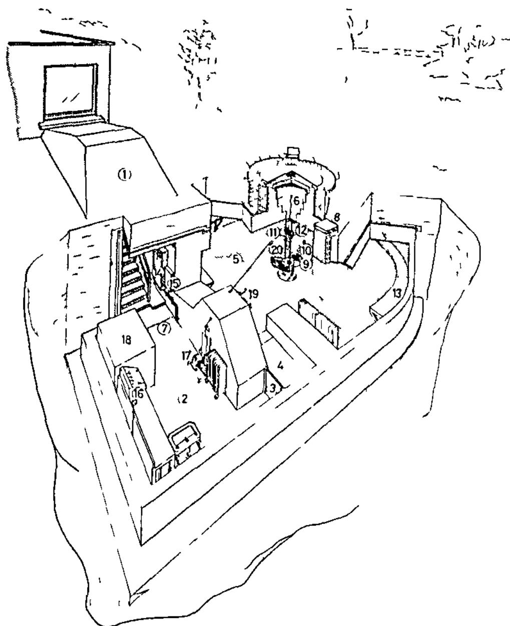


Fig 1 Irradiation premises for a 2 000 curie Cs unit 1 — entrance 2 — preparation room 3 — shielded door 4 — entry lock 5 — irradiation room 6 — concrete slab 7 — underground channel 8 — ventilation stack 9 — container 10 — central shelves 11 — sample holder 12 — rolling carrier 13 — wall shelves 14 — general electric panel 15 — control and safety rack 16 — control desk 17 — lift for motor 18 — refrigeration unit 19 — alarm signal 20 — source

gives access to the irradiation cell, from the adjoining preparation room via a built in entry having a width of 1 meter The electric winch which is used for raising the source, and the racks containing control and safety electro mechanical devices, are located in the preparation room This latter room also



Fig ? Device allowing ten small samples in test tubes to be irradiated at high dose rates (See text p 2?2)

contains a table a washstand connected to a well which is drained by an automatic pump a refrigeration unit and a switchboard for lighting heating and ventilation

An underground channel 0 4 × 0 2 m, joins the irradiation room with the preparation room Electric cables water pipes and an insulated duct permitting a refrigerant to be brought close to the container are accommodated in this channel Three oleothermic radiators fitted with thermostats provide a total heating power of 6 kW A vertical ventilator, mounted on a stack opening at the ground level above the irradiation room provides five air changes an hour

The source consists of compact CsCl sealed in a double stainless steel capsule Its radiochemical purity reaches 99 per cent and the gamma activity proportion $^{134}Cs/^{137}Cs$ is less than 5 per cent The total thickness of its walls and base amounts to 1 mm The effective height is 37 mm and the effective diameter 32 mm The source is screwed on and locked by a notched ring onto the container plug which thus functions as source holder

The *shielding container* which has also been used for shipment of the source is made of iron coated lead and is at least 170 mm thick The contact dose rate is 0 3 mR/hour The container weighs 700 kg the source holder plug included The latter and its opening into the container, is profiled according to two decreasing diameters in order to provide a safe free stroke during in

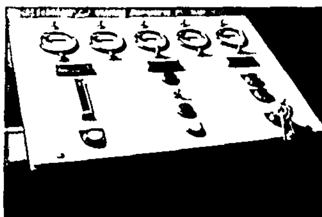


Fig. 3. Control board located in the preparation room

troduction and a precise final adjustment, thus reducing radiation leaks. The source holder plug weighs 10 kg.

Mechanical ancillaries. An electric winch, located in the preparation room, adjoining the irradiation cell, is used to lift the source holder plug by means of a cable and three intermediate pulleys. The cable in order to reduce back scatter, passes obliquely through the 0.8 m thick concrete wall between the irradiation cell and the preparation room. The source holder plug is screwed on to a rolling carrier, with which it forms a single moving body. The carrier moves between two vertical guide tubes which are fastened to the container and to the ceiling of the irradiation room. The normal up stroke is 0.45 meter.

An original device allows ten small samples in test tubes to be irradiated at high dose rates. This device is made of two sample holders which get close to the source when the latter rises exceptionally to 0.6 meter (Fig. 2). The sample holders are fastened to oscillating arms articulating with the guide tubes of the source holder plug. These arms keep the sample holders horizontal during the movement of approach which occurs when cams welded to the axis of the oscillating arms are actuated by the side wheels of the rolling carrier. The whole device, and particularly the shape of the cams, are designed in such a way that a blocking of the source during its down stroke is unlikely.

The *control board* (Fig. 3) is located in the preparation room. It includes an on-off key, a switch fixing the up stroke of the source (0.45 m or 0.6 m), push buttons operating the motor of the lift and panel lights indicating when the source moves and stops. There are five electric chronometers, automatically actuated by the source movements and permitting five workers independently to record the irradiation periods of their individual experiments.

Safety The thickness of the wall between the irradiation cell and the preparation room (0 8 m) the entry lock and other penetration channels (underground channel and cable duct) as well as the roof thickness are such that the dose in the neighbourhood of the irradiation room is negligible With the source in its container the surface dose rate is 0 3 mR/h

An electromagnetic safety circuit eliminates almost all irradiation hazards to careless workers The precautions taken to achieve this may be summarized as follows

The control board is set in operation by a contact key held by the single person appointed responsible

The source cannot be raised when the door of the irradiation room is open The door is automatically locked by the up stroke push button it becomes unlocked when the current is on Thus if the current fails the control board cannot be operated and the entry to the irradiation room is blocked In this case the source can be lowered in its container by disconnection of a bolt in the preparation room

Everybody entering the irradiation cell is supposed to operate a safety switch located in the entry lock, this prevents the raising operation Anyone who forgets this procedure will be warned of an eventual source elevation by an auditory alarm and will then be able to lower the source into its container and to unlock the door by operating the safety switch It should be noted that in case of need (e g current failure) the door may be unlocked manually from inside the cell

The dose rate at the periphery (i e 3 5 meter from the source) is as expected 60 R/h The dose rate in tubes put in the sample holders has been estimated by chemical dosimetry to be about 180 kR/h it is not completely homogenous Any desired dose rate between 180 kR and 60 R/h can be obtained by putting the organism or object at the required distance from the source which can easily be reproduced by preset reference marks on the roof of the cave Lower dose rates have been used for instance 1 6 R/h by BACQ & VAN CANEGHEM (1966) and may be obtained by suitable lead screening A large sector of the cave has been screened in such a way that the dose rate has been decreased by one hundredth

No difficulties have so far been encountered in the use of our ^{137}Cs irradiation facilities

Acknowledgements

The authors wish to thank P Van Caneghem and C Gerads for undertaking the dosimetric measurements Belgonucléaire in Bruxelles were responsible for the general conception of the irradiation premises with its ancillary facilities J Gillet the architect prepared the plans and the construction of the cave The technical bureau of the university under the direction of the late Professor Louis also collaborated in the project The source can be easily reached from a new laboratory of radiobiology planned by Mr Gillet

SUMMARY

The installation of a 2 000 curie cesium 137 irradiation unit at the Laboratoires de Radiobiologie is described The versatile premises aim at the promotion of scientific research in the fields of radiobiology and chemistry and have been in use since May 1965

ZUSAMMENFASSUNG

Der Bestrahlungsraum der Laboratoires de Radiobiologie fur die Behandlung mittels der neuen 2 000 curie Cesium 137 Strahlenquelle wird beschrieben Dieser praktische Raum zur Forderung der Forschung auf dem Gebiete der Radiobiologie und Chemie ist seit Mai 1965 im Betrieb

RÉSUMÉ

Description de la nouvelle cellule d irradiation par 2 000 curie de ^{137}Cs des Laboratoires de Radiobiologie Cette pièce a usages multiples destinée a faire avancer la recherche scientifique dans les domaines de la radiobiologie et de la radiochimie est en fonction depuis mai 1965

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FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR ASSOC PROF G HETTINGER) THE UNIVERSITY OF UMEA SWEDEN

AUTOMATIC ISODENSITY RECORDER FOR PHOTOGRAPHIC DOSIMETRY

by

C PETTERSSON

Much time can be wasted in determining the necessary isodose information for treatment planning in radiotherapy no matter what measurement technique is used A certain amount of automation is therefore desirable

Various types of automatic isodose recorders working with detectors — ionization chambers or scintillation detectors — in a phantom exposed to radiation have been described (KEMP 1946 HINE et coll 1950 MANCHEL & JOHNS 1954 SIMONS 1956 and LARSSON et coll 1963) Provided the relationship between the optical density and the absorbed dose is known to a sufficient degree of accuracy photographic dosimetry offers a two fold advantage in that the isodose information in one plane can be obtained by means of a single exposure while the actual exposure time is relatively short

Some sort of automatic apparatus for evaluating the material is necessary for the rational exploitation of photographic dosimetry A fully automatic isodensity recorder which has been specially developed to provide isodose curves for clinical use is described in this communication

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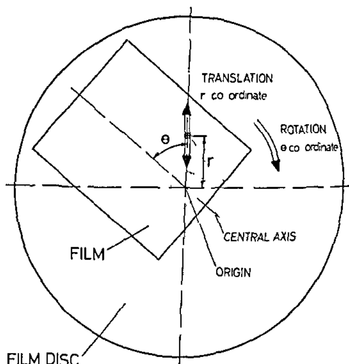


Fig 1 Schematic illustration of the co ordinate system used The θ co ordinate moves on with constant velocity while the r co ordinate is guided by a servo system so that the point of measurement moves along an isodensity curve

The principles of co ordinates Two different co ordinate principles are conceivable for representing isodose curves in one plane, cartesian (x, y) and polar (r, θ) co ordinates Isodose curves are easily represented by polar co ordinates when using a single field technique, while a combination of fields, on the other hand, often does not allow a suitable choice of the origin Under these circumstances the cartesian co ordinates are presumed to be preferable

If a technique with combination of fields is to be used, it will be most suitable to employ such a method of scanning the whole film by which both the x and y co ordinates move progressively (Gatzek et coll 1962, and Bogardus et coll 1965) With this method however, the isodose information is not obtained in the form of continuous curves

It is shown in Fig 1 how the films are arranged for transcription The circular disc rotates about its centre, which forms the origin of the co ordinate system The origin is set at the absorbed dose maximum and the θ co ordinate moves on with constant velocity while the r co ordinate is guided so that the point of measurement moves along an isodose curve

Construction of the recorder

The principles for both the mechanical and electronic construction of the recorder are apparent from Figs 2 and 3 The film is placed on one of the cir

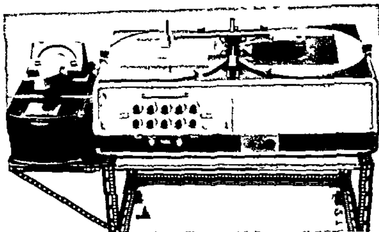


Fig 2 Front view showing the isodensity recorder control panel and the mechanical details The photographic film is placed on the circular disc to the right which has a transparent section of perspex the other disc is used for transcription

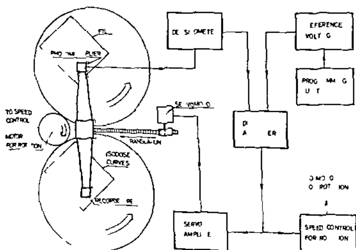


Fig 3 Schematic illustration of the principles of construction of the mechanical and electronic parts of the recorder The translation movements of the detector recorder arm are guided by a servo-control system while the rotation velocity of the discs is constant The density of the film is registered by a photomultiplier coupled to a commercial densitometer (Ansco MacBeth)

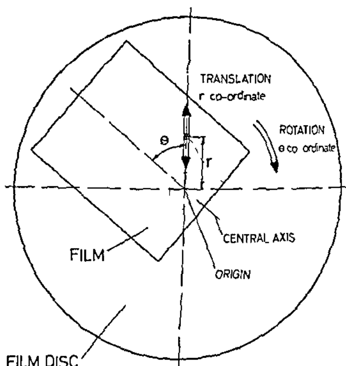


Fig. 1. Schematic illustration of the co-ordinate system used. The θ co-ordinate moves on with constant velocity while the r co-ordinate is guided by a servo system so that the point of measurement moves along an isodensity curve.

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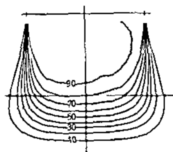


Fig 5 Comparison between isodensity curves at 30 MeV electron radiation field 13 cm × 13 cm evaluated by hand (o) and by the recorder The deviations fall within measurement accuracy

to be reversed for the transcription of the next isodose curve Time may thus be saved especially when dealing with electron isodoses where all the curves, from and including 90 % and less run along the front edge of the film

The control unit operating the arresting of the rotation consists of a sensitive polarized relay together with a special delaying circuit If the output from the difference voltage amplifier is too large the relay is activated and the motor that drives the disc is stopped until the servo motor again sets the density at the right value The sensitivity of this control unit can be adapted to meet the accuracy required of the isodensity curves The maximal sensitivity is circa 0 5 per cent of the density at the absorbed dose maximum The servo-control system may in certain cases not be able to keep the r co ordinate at the right value owing to the form of the isodose curves but because of the control unit the velocity of rotation need not be adjusted to the most difficult parts of the curve

The delaying circuit which forms an integral part of the control unit only operates during the transcription of those parts of the isodose curves where the absorbed dose gradient is large The servo-control system thus causes the density reading to oscillate around the correct value in such a way that the rotation is constantly stopped The delaying circuit has been so constructed that it operates when the voltage from the difference amplifier changes polarity periodically more often than about once every second

Stray light The arrangement for photometry i e the positioning of the light source and the photomultiplier together with the film is shown in Fig 3 The light source is similar to the one in the Ansco MacBeth densitometer but the arrangement for preventing stray light from reaching the photomultiplier has had to be improved The film is divided from the diaphragm by a perspex disc that carries the film the disc causes however the stray light to appear as an area of light around the measuring point and this disadvantage has been eliminated by adding diaphragms as seen in Fig 4

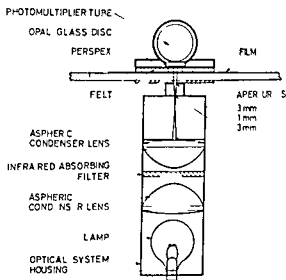


Fig 4 Schematic illustration of the photometric set up

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The density of the film is registered by a photomultiplier coupled to a commercial densitometer (Ansco MacBeth). The arm that carries the photomultiplier also carries the recording pen. The arm's translation movements during the recording are guided by a servo control system that determines the r coordinate and keeps the density constant while the discs rotate and the isodose curves are registered.

A voltage is obtained across a fixed resistor from the recorder connecting contact of the densitometer, and this voltage is compared with a reference voltage (which can be varied). The difference between these two voltages is amplified and then inducted to act both on a servo amplifier and a control unit, the rotation being stopped with the help of the latter if the density should deviate from the set level. The servo amplifier in turn operates the servo motor so that the difference in voltage becomes zero, i e the photomultiplier then moves along a curve on the film with a density analogous to the set reference voltage.

The reference voltage can be programmed by means of a number of helipots set at values corresponding to 90 %, 80 % of the absorbed dose at its maximum. The transition from one reference voltage to the next takes place via a step relay activated when one isodose curve is completed. The activation is set in motion by permanent magnets on the film disc, which close a magnetic reed switch. The magnets can be placed at will along the periphery of the disc so that it is possible to 'skip' part of the curves and allow the rotation

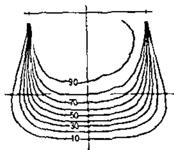


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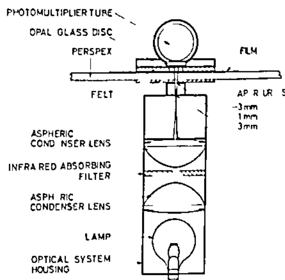


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A voltage is obtained across a fixed resistor from the recorder connecting contact of the densitometer, and this voltage is compared with a reference voltage (which can be varied) The difference between these two voltages is amplified and then inducted to act both on a servo amplifier and a control unit, the rotation being stopped with the help of the latter if the density should deviate from the set level The servo amplifier in turn operates the servo motor so that the difference in voltage becomes zero, i e the photomultiplier then moves along a curve on the film with a density analogous to the set reference voltage

The reference voltage can be programmed by means of a number of helipots set at values corresponding to 90 %, 80 % of the absorbed dose at its maximum The transition from one reference voltage to the next takes place via a step relay activated when one isodose curve is completed The activation is set in motion by permanent magnets on the film disc, which close a magnetic reed switch The magnets can be placed at will along the periphery of the disc so that it is possible to 'skip part of the curves and allow the rotation

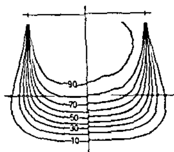


Fig 5 Comparison between isodensity curves at 30 MeV electron radiation field 13 cm × 13 cm evaluated by hand (o) and by the recorder The deviations fall within measurement accuracy

to be reversed for the transcription of the next isodose curve Time may thus be saved especially when dealing with electron isodoses where all the curves from and including 90 % and less, run along the front edge of the film

The control unit operating the arresting of the rotation consists of a sensitive polarized relay together with a special delaying circuit If the output from the difference voltage amplifier is too large, the relay is activated and the motor that drives the disc is stopped until the servo motor again sets the density at the right value The sensitivity of this control unit can be adapted to meet the accuracy required of the isodensity curves The maximal sensitivity is circa 0 5 per cent of the density at the absorbed dose maximum The servo control system may in certain cases not be able to keep the r co-ordinate at the right value owing to the form of the isodose curves but because of the control unit the velocity of rotation need not be adjusted to the most difficult parts of the curve

The delaying circuit which forms an integral part of the control unit only operates during the transcription of those parts of the isodose curves where the absorbed dose gradient is large The servo-control system thus causes the density reading to oscillate around the correct value in such a way that the rotation is constantly stopped The delaying circuit has been so constructed that it operates when the voltage from the difference amplifier changes polarity periodically more often than about once every second

Stray light The arrangement for photometry i e the positioning of the light source and the photomultiplier together with the film is shown in Fig 3 The light source is similar to the one in the Ansco MacBeth densitometer but the arrangement for preventing stray light from reaching the photomultiplier has had to be improved The film is divided from the diaphragm by a perspex disc that carries the film the disc causes however the stray light to appear as an area of light around the measuring point and this disadvantage has been eliminated by adding diaphragms as seen in Fig 4

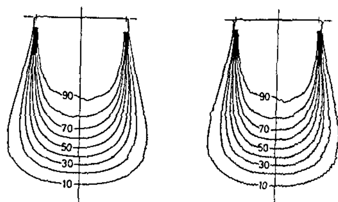


Fig. 6. Isodensity curves at 33 MeV electron radiation, field 8 cm × 8 cm, recorded with different rotation velocities. The time intervals for the evaluation were 15 min (left) and 9 min (right), respectively.

The stray light that passes in through the perspex disc between the felt cushions does not appear to affect the photometric result. A check with a density wedge disclosed that a density up to at least 3 O.D.U. can be measured correctly. Furthermore, a comparison between isodensity curves evaluated by hand and by the recorder revealed that the disc did not influence the recording. Fig. 5 shows this comparison both along the central axis and at right angles to it; the deviations lie within measurement accuracy.

Choice of diaphragm size. The size of the diaphragm has been selected so that the optical density is integrated over a film area of about 2 mm diameter. A smaller diaphragm gives better resolution so that small inhomogeneities in the film appear. When dosimetric films are evaluated for field sizes that show up under electron treatment, a resolution corresponding to the 2 mm opening in the diaphragm is fully sufficient.

To increase the opening, on the other hand, is not to be recommended if great density gradients are evident, since then faults in reproduction will appear. In extreme cases, e.g. when the front edge of the film is being read, the isodose curves are displaced a distance corresponding to up to a half of the diaphragm opening towards a higher density value. This can be explained in the following way. The registered density is logarithmically dependent on the flux of light through the film. The mean density integrated over a surface corresponding to the diaphragm opening is consequently not linearly dependent on the mean flux of light through the same surface.

Analysis indicates that the displacement of the diaphragm centre in extreme cases is about 0.7 r towards higher density areas where r equals the radius of the diaphragm opening. In photometry, where the geometrical accuracy needs to be better than 1 mm, the radius of the diaphragm may consequently be at the most $\frac{1}{0.7} = 1.5$ mm.

Correction for the optical density intercept When evaluating films for dosimetric purposes it must be observed that the optical density is not proportional to the absorbed dose even after the zero dose density has been subtracted from the observed density Special tests must therefore be made to determine the relationship between the absorbed dose and the density which is linear under certain conditions (HETTINGER & SVENSSON 1967) and then the density at the zero dose, the density intercept can be determined When using the isodensity recorder it is necessary that a separate adjustable reference voltage be added to all reference voltages as a correction for the intercept and to ensure a simple adjustment with an isodensity percentage that can be directly read off on the helipots The intercepts corresponding to density values between 0 and 0 6 may thus be eliminated

Results Some examples of isodose curves are given in Fig 6 The appearance can be regulated with three parameters the sensitivity at the servo amplifier and the sensitivity at the control unit together with the velocity of rotation

Acknowledgement

The work was supported by grants from the Swedish Cancer Society

SUMMARY

An automatic isodensity recorder giving optical density readings in the form of continuous curves is described It was designed chiefly for use in the evaluation of dosimetric films in the clinic and for regular control of the radiation fields of accelerators

ZUSAMMENFASSUNG

Beschreibung eines automatischen Aufzeichners für kontinuierliche Isodensitätskurven Das Instrument ist hauptsächlich für die klinische Auswertung von Dosimetriefilmen und für die regelmässige Kontrolle der Strahlenfelder von Elektronenschleudern gedacht

RÉSUMÉ

L'auteur décrit un enregistreur automatique d'isodensité donnant les mesures de densité optique sous forme de courbe continue Il est destiné principalement à l'étude de films dosimétriques pour les besoins cliniques ainsi qu'au contrôle régulier des champs d'irradiation des accélérateurs

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FROM THE DEPARTMENT OF RADIOTHERAPY B UNIVERSITEITSKLINIEKEN ST RAFAEL, LEUVEN BELGIUM

ISODOSE CHARTS FOR CURVED SURFACES IN TELECOBALT AND TELECESIUM THERAPY

by

J M DEBOIS

The surface of skin to be irradiated is often not a plane surface, typical examples are the head neck and thorax Generally however the isodoses available in a department of radiotherapy all apply to flat horizontal surfaces To enable the use of such isodose charts tissue equivalent material may be placed over the skin of the patient but the skin sparing effect will be lost in telecobalt and telecesium therapy There are two ways of making the correction for the isodose distribution at curved surfaces

Individually designed filters of aluminium or other metals matching the tissue deficiencies of the subject relative to a horizontal surface have been described in detail by different authors (HALL & OLIVER 1962 SUNDBOM 1964 1965 and VAN DER GEYN 1965) The filter is placed near the end of the collimator in order to preserve the skin sparing effect in telecobalt radiation These methods require however special technical possibilities that are not always at hand in a radiotherapy department

Normal isodoses can be transformed to true isodoses for any irregular or convex surface by calculations usually referred to as corrections for lack of

Submitted for publication 18 April 1966

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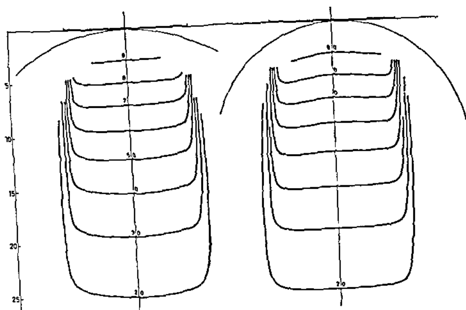
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F 3 Influence of the surface form on the dose distribution at telecobalt irradiation field 8 cm × 8 cm SSD 80 cm

is how to obtain a curved surface in a water tank For this purpose we have deviced a simple and reliable method for obtaining curved water surfaces the device has enabled us to study the isodose distributions with our automatic isodose plotter Some results obtained with telecobalt and telecesium beams are reported in the present paper

Material and Methods The curved surface is obtained by fabricating a plexiglass box with a curved bottom (Fig 1) The box is fitted in the water tank as seen in Fig 2 We have made three different boxes having cylindrical surfaces of the following radii 6 5 *cm* 12 5 cm and 17 cm respectively These radii match approximately the shapes of the average head and neck and thoracic and abdominal outlines The plexiglass has a thickness of 5 mm The box is so fixed in the *phantom* that the water level in the tank coincides with the upper central surface of the plexiglass bottom of the box

The radiation beams investigated were from a telecobalt apparatus Barazzetti Jupiter Senior (SSD 80 cm) and a Siemens Gammatron 2 (SSD 50 cm) The telecesium beam was a Barazzetti Caesapan unit (SSD 30 cm) The isodoses were obtained with an automatic isodose plotter (DE ROO et coll



Fig 1 The plastic box with half cylindrically curved bottom

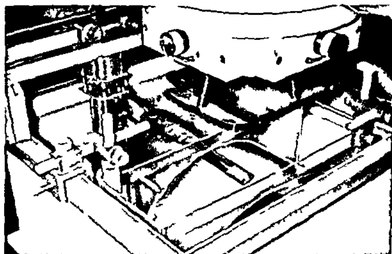


Fig 2 Experimental set up the plastic box being placed in the water phantom

bolus' or tissue deficiency Johns (1961) has given the correction factor of 5 5 % per cm for telecobalt and 6 % per cm for telecesium radiation

Ambesi Impiombato et coll (1959) have published an extensive graph giving the correction factors for any tissue deficiency or surplus relative to the ideal 'horizontal' surface Dutreix & Dutreix (1962) have demonstrated that a shift of the isodose curve over a distance of 2/3 the tissue deficiency or surplus, is not far away from the true distribution This method has also the advantage of being very speedy As far as we know, isodose charts for curved surfaces have not been published or made available The difficulty presenting itself

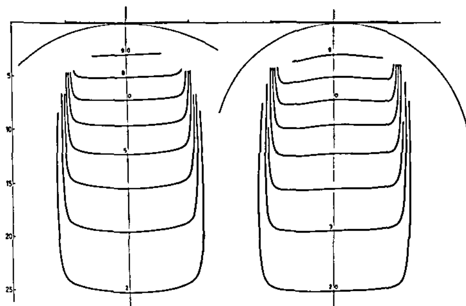


Fig 3 Influence of the surface form on the dose distribution at telecobalt irradiation field 8 cm 8 cm SSD 80 cm

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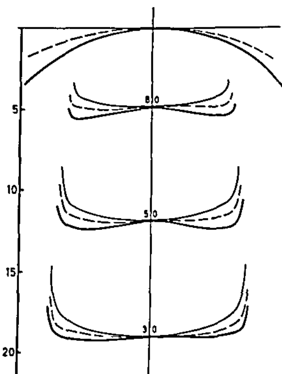


Fig 4 Composite graph of isodose shift for a 12 cm × 12 cm field at telecobalt irradiation SSD 80 cm

1966), and the phantom was a water tank of size 50 cm × 50 cm, depth 80 cm (semi infinite)

The calibration was carried out for a depth of 5 cm according to MEREDITH (1963) We have presumed that the central axis depth dose of a normal standard field remains unaffected in the presence of a curved surface, and this was confirmed in the comparison made between different axis depth doses in the present study

Results and Discussion

The extent of displacement of the isodose curves will be determined by the tissue deficiency and the absorption characteristics of the radiation According to the correction values given by JOHNS, the dose value at any given point has to be corrected, so that, for instance, a 50 % value will become 52 25 % for a 'tissue deficiency of half a centimeter The new isodose curve of 50 % for the curved surface will be deeper than for a plane surface The overall influence of the curved surface is a corresponding displacement of the isodose curve to a lower depth The displacement is in fact a result of the circumstance that the absorption is less just beneath a plane surface implying that more

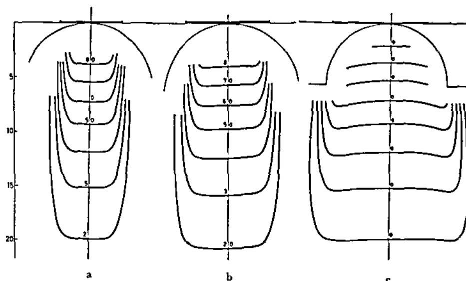


Fig 5 Influence of field size on the displacement of the isodose lines for a given surface shape telecobalt irradiation SSD 50 cm a) Field 6 cm × 6 cm b) field 8 cm × 8 cm and c) field 125 mm × 125 mm

photons penetrate deeper When the curved surface has a nearly circular shape as the neck for example the tissue deficiency is progressively greater towards the edges of the beam in case the beam is centered towards the highest point of the surface The correction has consequently to be progressively greater from the axis towards the edges of the beam and the resulting dis placement together with the shape of the surface and field size determine the overall aspect of the isodose curves

A Telecobalt The influence of the surface form for a field 8 cm × 8 cm is shown in Fig 3 In Fig 4 several isodoses have been assembled in a compo site graph in order to show more clearly the shapes of isodose curves obtained The influence of different field sizes for one shape of surface is illustrated in Fig 5 Almost no modifications have to be made for small fields because of the minute tissue deficiency the tissue deficiency becomes however more important for larger fields and the displacements will be more marked

The following ranges of correction factors were obtained

5 % to 8 % per centimeter for 80 cm SSD

3 % to 6 % per centimeter for 50 cm SSD

depending on field size and distance from the axis For larger fields and regions

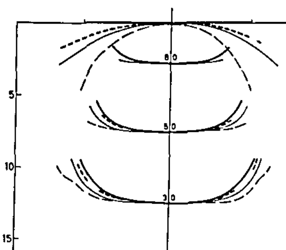


Fig 6 Composite graph showing the isodose shift for a 12 × 12 cm field with telecesium radiation SSD 30 cm

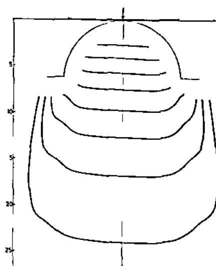
near the axis, the correction values will be smaller The value of 5 5 % proposed by JOHNS (1961) seems to constitute a good mean value The method of shifting the isodoses according to DUTREIX & DUTREIX (1962) yields only a good approximation, since the shifting distance is by no means constant from surface to depth

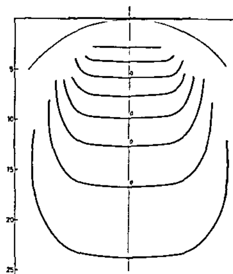
B Telecesium The isodoses for telecesium below plane surfaces have typically rounded shape, this is because the diameter of the source is large, which results in quite a large geometric and total penumbra The central part of the beam, in comparison with a telecobalt beam, has a much more rounded shape

A composite graph of some isodose charts for telecesium radiation and a 12 cm × 12 cm field is shown in Fig 6 The effect on the isodose curve will be that the typically rounded shape becomes more horizontal (Fig 7) This shift may be considered as an advantage in the sense that a more homogeneous dose distribution is obtained

Looking for a correction factor we obtained a rather large range, even more extensive than for telecobalt, from 3 % up to 10 % depending on field size and distance from the axis At some distance from the axis on a line parallel to it, even a progressive decrease was found which means that a mean value of 6 % only provides an approximation

The fact is that the isodose distributions should be measured, since theoretical calculations only give a rough idea of the true distribution, for telecesium in particular





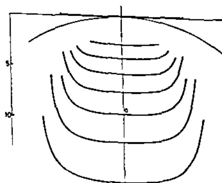


Fig 7 I odoses for the d fferent curved surfaces using the telecesium rad ation beam SSD 30 c n 12 cm × 12 cm field Surf ces of 6 5 cm rad us (a) 12 5 cm (b) and 17 cm rad us (c) (Cf text on p 235)

(Cop es of the isodose charts (only square fields) a e ava l ble at easonable cost from the autho)

SUMMARY

Isodose charts for curved surfaces irradiated with telecobalt and telecesium beams have been prepared by measurements with an automatic isodose plotter beneath a convex surface in a water phantom The values thus obtained were compared with the theoretically deter mined values

ZUSAMMENFASSUNG

Isodosenkurven bei Telekobalt und Telecesium Bestrahlung von krummen Oberflachen wurden in einem Wasserphantom und mit Hilfe einer automatischen Registrierungsvorrich tung bestimmt Die Ergebnisse sind mit den theoretisch bestimmten Werten verglichen worden

RÉSUMÉ

Des courbes isodoses sous surfaces courbées ont été tracées avec l aide d un inscripteur automatique et mesurées dans un fantome d eau pour les rayonnements de télécobalt et télécésium Les resultats sont comparés aux courbes déterminées theorétiquement

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CONTRIBUTION DE L'HOPITAL DA CRUZ VERMELHA BRASILEIRA RIO DE JANEIRO BRASIL ET DU DEPARTEMENT DE PHYSIOLOGIE FACULTE DE MÉDICINE DE L'UNIVERSITÉ DE MONTREAL QUÉBEC CANADA

L'OBTENTION PREALABLE DES ISODOSES POUR TELECOBALT THERAPIE EN COURONNE

par

A F G DA ROCHA et J M LEGARE

Parmi les nombreuses techniques utilisees en radiotherapie cinetique se trouve la cyclotherapie en couronne MARQUES et ses collaborateurs (1950 1958) ont souligne son utilité en roentgen therapie Depuis l avenement des appareils de cobalt 60 en télégamma therapie on a cherche a appliquer cette technique rotatoire Comm nous verrons plus loin au point de vue la réparti tion de la dose il est avantageux de se servir de la double couronne pour traiter les lesions profondes en effet cette technique permet de ceder moins de 30 a 40 % de la dose tumorale a la peau et au tissu sous cutane tout en ayant une distribution désirée a la tumeur Nous nous sommes servis avec avantage de la telecobalt therapie en couronne dans des traitements définitifs et palliatifs des neoplasies de la vessie des poumons du rein etc

La cyclotherapie en couronne est appelée ainsi en raison de la forme de couronne des tissus irradies autour de l axe de rotation En pratique on peut arriver exactement au meme mode de traitement de deux façons differentes soit que la table ou la chaise pivote sur elle m me (Fig 1a) soit que la source

Soumis a la Rédaction le 20 décembre 1965

SUMMARY

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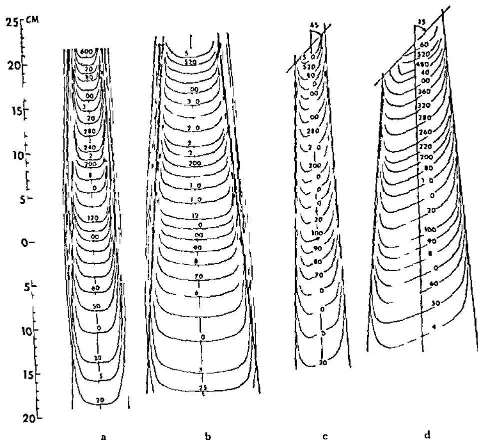


Fig 2 Isodoses de b se pour un appa e l de cobalt 60 fonct onnant à une DSC de 60 cm a) et b) Champs perpe dicula res de 5 et d 10 cm de d amètre pour un mannequin infin c) et d) Champs bl ques (α = 45) de 5 et de 10 m d d amètre pour un mannequin infin

L aire du champ a divers niveaux sous la p au est choisie comme une ellipse parfaite

L agrandissement de l ellipse est negligeable pour les fins de calculs de la fraction de temp (choisie 0/180 = 20/360) durant laquelle un point de tissu est expose a cette ellip e Pour les calculs on choisit arbitrairement l ellipse hori zontale passant par le point de rencontre de l axe central du champ et de l axe de rotation

La dose a un niveau donn a l interieur des limites laterales du champ est celle de l axe central En dehors du champ on suppose que la dose tombe brusque ment a zéro

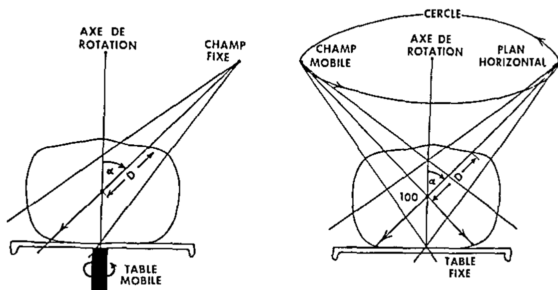


Fig 1 Deux méthodes équivalentes d obtention de la télécobalt thérapie en couronne L angle d incidence α demeure constant au cours du traitement

tourne circulairement dans un plan horizontal autour de l'axe vertical (Fig 1b) La technique de la chaise pivotante est probablement la plus utilisée en radiothérapie rotatoire et pendulaire L'angle α entre l'axe vertical et l axe central du champ demeure constant au cours du traitement Il en est de meme pour la grandeur du champ au centre de rotation, pour la distance source centre (DSC) et pour la distance peau centre (DPC) Comme nous le verrons, lorsque la DPC (niveau sous la peau) varie au cours d une rotation, il est préférable de combler les tissus superficiels afin d obtenir une couronne parfaite à la face d entrée

Le présent travail a pour but d'établir préalablement les isodoses issues de la télécobalt thérapie en couronne simple et double, ceci facilite ainsi les calculs aux utilisateurs de cette technique et permet de comparer les résultats a ceux des techniques courantes

Méthode de l'obtention des isodoses

A titre d exemple, choisissons un appareil de cobalt 60 fonctionnant à des grandeurs de champ de 5 et de 10 cm de diametre a une DSC de 60 cm L'angle d incidence α choisi dans ce travail est de 45°

A *Méthode simplifiée* Dans cette méthode (Tableau A et Fig 3), nous faisons les simplifications suivantes

Tableau *(cont)*

O	A	B	C	D	E
70	70	70	70	70	70
92	133	180	180	180	118
36	52	70	70	70	46

O	A	B	C'	D	E
70	73	76 a chacun des angles	75 a chacun des angles	72	67
70	73			72	67
70	73			72	67
70	73			72	67
69	73			72	67
68	73			72	66
68	73			71	65
67	73			70	64
67	73			69	63
67	74			69	63
67	75			70	63
68	75			70	63
69	75			73	63
69	75			72	62
70	75			73	58
70	75			74	50
70	75			75	49
1169	1256			1217	1064
1169	1256			1217	1064
70	75			72	67
70	73			75	48
2478	2660			2581	2243
69	74	76	75	71	62

etre paralleles a la peau (Fig 2) Aussi le surdosage pour une demi rotation de l ellipse en un point est souvent compense par le sous dosage de l autre demi rotation

Les étapes pour obtenir les isodoses par cette methode (Fig 3) sont les suivantes

Tracer le champ y compris la surface d entree, l axe de rotation et les rayons émanant de la source (Fig 3) Ces rayons E D C O C D,

Tableau

La dose aux points du plan situé à 18 cm sous la peau (Figs 3 et 5) telle qu'obtenue en télécobalt thérapie en couronne. Le diamètre du champ à une DSC de 60 cm est de 10 cm. L'angle d'incidence α est de 45°. Les résultats finals se trouvent à la dernière rangée.

A. Méthode simplifiée

Point	I	D	C	B	A
Dose de l'axe central	70	70	70	70	70
θ	0	23	40	55	72
θ × 70/180	0	8.9	15.5	21	28

B. Méthode améliorée

Rayon	I	D	C	B	A
170	33	52	58	62	67
160	30	52	58	62	67
150	10	38	56	62	67
140	5	10	47	61	67
130	3	2	21	58	67
120	1		10	40	63
110				26	62
100				18	60
90				10	56
80					53
70					53
60					51
50					49
40					43
30					35
20					27
10					21
Somme (10° à 170°)	82	154	250	399	908
Somme (190° à 350°)	82	541	250	399	908
0°					20
180°	34	52	58	62	67
Grand total	198	360	558	860	1903
Grand total/36	5.5	10.0	15.5	36	52

L'aire à un niveau donné est en réalité une ellipse déformée. De ce fait, le centre de l'ellipse est quelque peu déplacé latéralement (Fig. 3). L'erreur introduite en choisissant une seule ellipse est faible en raison de la faible divergence du faisceau sauf pour les points des rayons E et E (Fig. 3). Ces points devraient se trouver aux extrémités du grand axe de l'ellipse. En ce qui a trait à la dernière simplification, l'erreur n'est pas aussi grande qu'elle puisse paraître au premier abord. En effet, les isodoses d'un champ oblique ont tendance à

Tableau *(cont)*

O	A	B	C	D	E
70	70	70	70	70	70
9[illegible]	133	180	180	180	118
36	52	70	70	70	46

O	A	B	C	D	E
70	73	76	75	72	67
70	73	à chacun	à chacun	72	67
70	73	des angles	des angles	72	67
70	73			72	67
69	73			72	67
68	73			72	66
68	73			71	6[illegible]
67	73			70	64
67	73			69	63
67	74			69	63
67	75			70	63
68	75			70	63
69	75			73	63
69	75			72	6[illegible]
70	75			73	58
70	75			74	50
70	7[illegible]			7[illegible]	49
1169	1256			1217	1064
1169	1256			1217	1064
70	75			72	67
70	73			75	48
[illegible]478	2660			2581	2243
69	74	76	75	71	62

etre paralleles a la peau (Fig 2) Aussi le surdosage pour une demi rotation de l ellipse en un point est souvent compense par le sous dosage de l autre demi rotation

Les etapes pour obtenir les isodoses par cette methode (Fig 3) sont les suivantes

Tracer le champ y compris la surface d entrée l axe de rotation et les rayons emanant de la source (Fig 3) Ces rayons E D C O C D,

Tableau

La dose aux points du plan situé à 18 cm sous la peau (Figs 3 et 5) telle qu'obtenue en télécobalt thérapie en couronne Le diamètre du champ à une DSC de 60 cm est de 10 cm L'angle d'incidence α est de 45 Les résultats finals se trouvent à la dernière rangée

A Méthode simplifiée

Point	L	D	C	B	A
Dose de l'axe central	70	70	70	70	70
θ	0	23	40	55	72
$\theta \times 70/180$	0	8 9	15 5	21	28

B Méthode améliorée

Rayon	I	D	C	B	A
170	33	52	58	62	67
160	30	52	58	62	67
150	10	38	56	62	67
140	5	10	47	61	67
130	3	2	21	58	67
120	1		10	10	63
110				26	62
100				18	60
90				10	56
80					53
70					53
60					51
50					49
40					43
30					35
20					27
10					21
Somme (10 à 170)	82	154	250	399	908
Somme (190 à 350)	82	541	250	399	908
0					20
180	34	52	58	62	67
Grand total	198	360	558	860	1903
Grand total/36	5 5	10 0	15 5	36	[illegible]

L'aire à un niveau donné est en réalité une ellipse déformée, de ce fait le centre de l'ellipse est quelque peu déplacé latéralement (Fig 3) L'erreur introduite en choisissant une seule ellipse est faible en raison de la faible divergence du faisceau sauf pour les points des rayons E et E (Fig 3) Ces points devraient se trouver aux extrémités du grand axe de l'ellipse En ce qui a trait à la dernière simplification, l'erreur n'est pas aussi grande qu'elle puisse paraître au premier abord En effet les isodoses d'un champ oblique ont tendance à

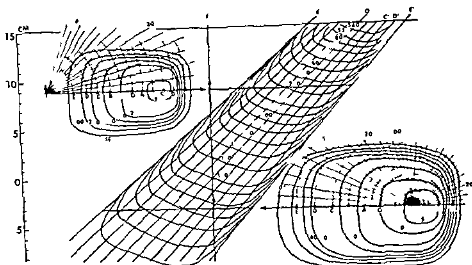


Fig 5 Méthode amél orée de calculer les isodoses exactes et préalables en thérapie en couronne simple (Tableau B) Les isodoses a divers ni eaux ($P = 6$ et 18 cm) s obtiennent a partir des valeurs du grand axe au champ obl que illustré et du petit axe du champ perpend cula re (fig 2b) pour la même distance de l axe central

E passent a diverses distances que l on détermine p rp ndiculairement a l axe central a 60 cm de la source de cobalt 60

Obtenir la dose de l axe central du champ immobile (Tableau A)

Tracer une ellip e typique (celle du centre de rotation) a partir de son équa tion et localiser le centre de cette ellip e (ligne pointillee de la Fig 3)

Obtenir $\theta/180$ et la dose en divers points (Tableau A) de chacun des niveaux sous la peau

Pour un rayon emanant de la source placer sur l ordonnee logarithmique les valeurs de la dose finale (dose de l axe central $\times$ $\theta/180$) en fonction du niveau dans le corp sur l abscisse linéaire Répeter pour les rayons E D C O C D E

Interpoler sur ces courbes les points indiquant 200 % 180 % 160 % 60 % 50 % et 40 % afin d obtenir les isodoses desirees

Faire le tracé des isodoses sur papier de soie superposé au papier millimetrique de la Fig 3 Se servir de la symetrie de chaque coté de l axe de rotation pour reduire les erreurs experimentales des deux cotes Resultat final Fig 4

B *Méthode ameliorée* Cette methode a comme etapes

Obtenir les isodoses du champ oblique (Fig 2 c et d)

Tracer les isodoses réelles a divers niveaux (exemple a 6 et a 18 cm de la

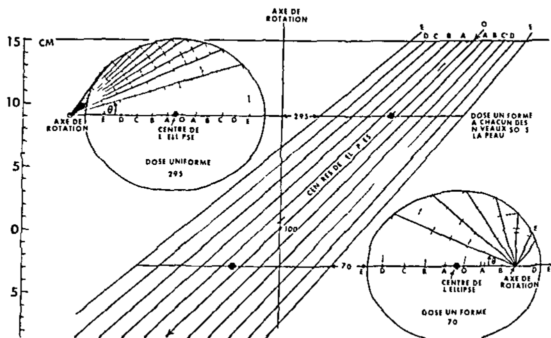


Fig 3 Méthode simplifiée pour calculer les isodoses en thérapie en couronne (Tableau A) Les ellipses de dose uniforme utilisées à des profondeurs P de 6 et de 18 cm sont choisies comme celles passant au niveau du centre de rotation

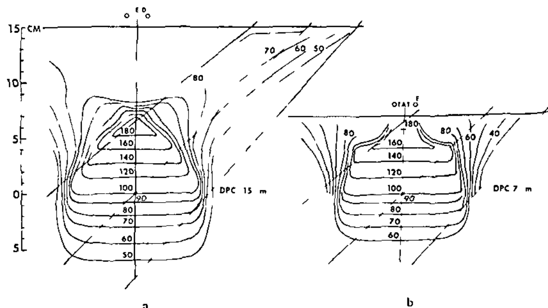


Fig 4 Isodoses issues de la télécobalt thérapie en couronne simple (DSC = 60 cm a = 45 cm diam = 10 cm) Les résultats sont presque identiques que la profondeur P soit de 15 cm (a) ou de 7 cm (b) Les isodoses sont donc calculées préalablement (a)

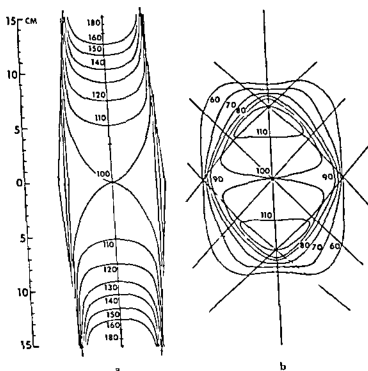


Fig 7 Comparison des d st but ons préalables des isodoses de deux ch mps en sens nv e (a) et de la telécobalt thérapie en couronne double (DSC = 60 cm d am = 10 cm α = 45) pa la methode simpl fiée (b)

La méthode de Du Sault & Legare (1963) permet d obtenir les isodoses des champ obliques (Fig 2 c et d) a partir des champs perpendiculaires avec precision sauf dans la région de la penombre Une autre methode d obtention rapide s appuyant sur les correctifs d absorption plutot que sur les rapports tissu air qui tiennent compte de l absorption et des differences de diffusion a ete avancee par Campbell & Tan Thun (1964) Les résultats sont assez voisins

Thérapie en couronne (*methode simplifiee*) La figure 4 (a et b) illustre les resultats que l on obtient (Tableau A) en telécobalt therapie en couronne pour un appareil fonctionnant a une DSC de 60 cm En comparant les Tableaux A et B et a la figure 4a on voit que les rayons E D C B et A se trouvent en dehors de la région d interet à cette profondeur de 18 cm sous la peau On constate aussi que les ecarts qui paraissent éleves a cette profondeur (Tableau A)

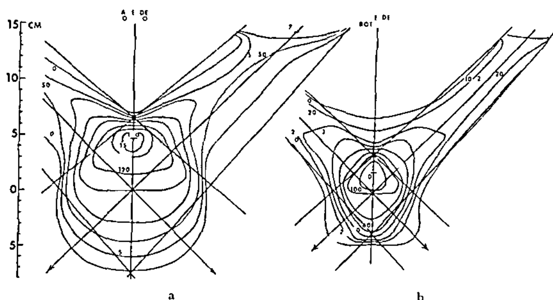


Fig 6 Isodoses préalables pour la therapie en couronne simple par la methode amelioree (DSC = 60 cm $\alpha = 45$) Les diamètres du champ sont de 10 cm (a) et de 5 cm (b)

Fig 5) du champ oblique immobile à partir des valeurs du petit axe du champ perpendiculaire (Fig 2, a et b) ainsi que des valeurs du grand axe du champ oblique de la figure 2 (c ou d)

Prendre la moyenne des contributions de dose (Tableau B) pour chacun des points E, D, C, O C, D, E'

Tracer sur papier semi logarithmique les valeurs de la dose pour le rayon E en fonction du niveau sous la peau Répeter pour les autres rayons

Interpoler à toutes les dix ou vingt unites pour obtenir les isodoses voulues (Fig 6) Celles ci sont independantes du lieu de la face d entrée

Resultats

Isodoses des champs perpendiculaires et obliques La figure 2 represente les isodoses de base des champs perpendiculaires et obliques d'un mannequin infini Les diametres de ces champs a une DSC de 60 cm sont de 10 et de 5 cm

Les isodoses des champs perpendiculaires (Fig 2, a et b) s obtiennent à partir de l extrapolation appropriee (LEGARE 1964b) des isodoses fournies apres que la dose de l axe central ait ete calculé pour le mannequin infini (LEGARE 1964a) Ces dernieres isodoses n etaient donnees que jusqu à 10 cm en deçà du centre de rotation, et ce, pour un fantome semi infini

La dose de l axe central d un champ oblique est celle du champ perpendiculaire à la peau (Fig 2, a et b) pourvu que l angle α soit inférieur a 15°

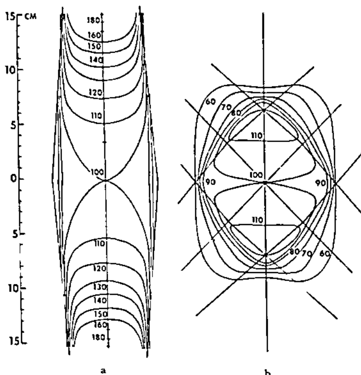


Fig 7 Comparaison des distributions préalables des isodoses de deux champs en sens inverse (a) et de la télécobalt thérapie en couronne double (DSC = 60 cm d m = 10 cm α = 45) par la méthode simplifiée (b)

La methode de Du Sault & Legare (1963) permet d obtenir les isodoses des champ obliques (Fig 2 c et d) a partir des champs perpendiculaires avec precision sauf dans la region de la penombre Une autre methode d obtention rapide s appuyant sur les correctifs d absorption plutot que sur les rapports tissu air qui tiennent compte de l absorption et des differences de diffusion a eté avancee par Campbell & Tan Thun (1964) Les resultats sont assez voisins

Therapie en couronne (methode simplifiee) La figure 4 (a et b) illustre les resultats que l on obtient (Tableau A) en télécobalt therapie en couronne pour un appareil fonctionnant a une DSC de 60 cm En comparant les Tableaux A et B et à la figure 4a on voit que les rayons E D C B et A se trouvent en dehors de la région d intéret a cette profondeur de 18 cm sous la peau On constate aussi que les écarts qui paraissent eleves a cette profondeur (Tableau A)

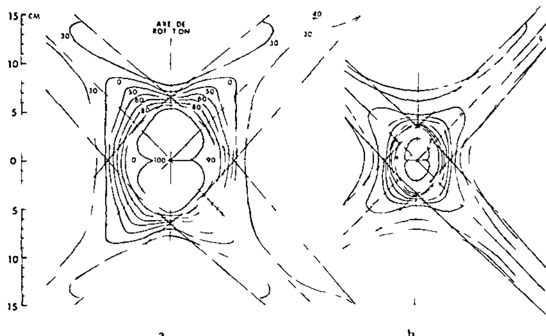


Fig. 8. Isodoses réelles préalables pour la télécobalt thérapie en couronne double par la méthode améliorée (DSC = 60 cm, α = 45°). Les diamètres du champ sont de 10 cm (a) et de 5 cm (b).

sont en réalité très réduits (Fig. 4a) lorsqu'on se sert de la symétrie. L'effet de l'épaisseur du tissu importe peu sur la distribution de la dose. Ceci résulte des deux faits suivants : la distribution de la dose des derniers centimètres de tissu sur l'axe central d'un mannequin fini varie peu en fonction de l'épaisseur réelle du tissu (LEGARÉ 1966) utilisé ici en télécobalt thérapie, les valeurs de l'axe central et des isodoses d'un champ perpendiculaire (BRAESTRUP & MOONEY 1958, DU SAULT 1959, LEGARÉ 1964a) sont presque identiques pour les mannequins semi-infinis et infinis. Dans le présent travail, on a trouvé que l'on peut aussi tracer d'avance les isodoses des champs obliques simples ou multiples. Les seuls écarts d'isodoses entre les deux sortes de 'fantome' se trouvent aux 3 à 4 premiers centimètres de tissu, cet écart diminue à mesure que le champ diminue de taille.

La fraction de temps $\theta/180° = 2\theta/360°$, durant laquelle un point est irradié, est un facteur géométrique indépendant du tissu (Fig. 3).

Les isodoses (Fig. 4a) issues sont indépendantes de la DPC pourvu que la DSC demeure constante (60 cm ici). Les centimètres de tissu le long de l'axe central entre son point d'entrée et le centre de rotation ne servent qu'à ajuster le temps d'exposition pour exposer le centre de rotation à 100 R. Ceci s'obtient

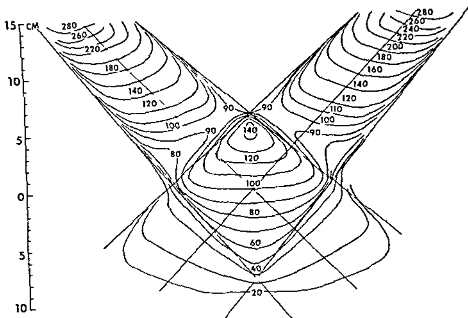


Fig 9 Isodoses preal bles de deux champs obliques (DSC = 60 cm α = 45 diam = 10 cm)

a partir du taux (R/mn) dans l air et du rapport T/A pour cette distance *D* sur l axe central et pour le champ au centre de rotation

La figure 7b illustre l avantage dosimetrique de la double couronne sur les isodoses provenant de deux champ en sens inverse (Fig 7a) La dose est plus faible a la peau et au tissu sous cutane parce qu en therapie en couronne ces tissus sup rficiels ne sont exposes que pour un instant a chaque rotation

Comme on le verra les isodoses telles qu obtenues par cette methode ne sont pas de haute precision Pour obtenir les isodoses reelles on doit se servir de la methode amelioree qui suit

Therapie en couronne (methode amelioree) Tout comme dans la methode simplifiee les isodoses sont calculees au prealable (Tableau B) et s appliquent donc a toutes les epaisseurs de tissu Il suffit de superposer la coupe du patient sur les isodoses obtenues Ceci s applique aussi bien a la couronne simple (Fig 6) qu a la double couronne (Fig 8)

La couronne simple (Fig 6) contrairement a deux champs obliques (Fig 9) ayant le meme angle α a la face d entree permet d exposer les premiers centimetres de tissu a un faible niveau tout en donnant une dose tumorale voulue

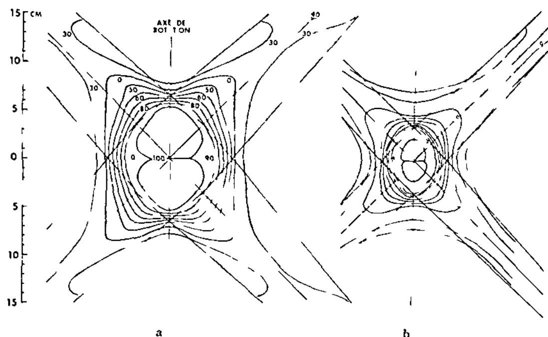


Fig 8 Isodoses réelles préalables pour la télécobalt thérapie en couronne double par la methode améliorée (DSC = 60 cm α = 45) Les diametres du champ sont de 10 cm (a) et de 5 cm (b)

sont en réalité tres reduits (Fig 4a) lorsqu on se sert de la symétrie L effet de l épaisseur du tissu importe peu sur la distribution de la dose Ceci resulte des deux faits suivants la distribution de la dose des derniers centimetres de tissu sur l axe central d un mannequin fini varie peu en fonction de l épaisseur réelle du tissu (LEGARE 1966) utilisé ici en télécobalt therapie, les valeurs de l'axe central et des isodoses d un champ perpendiculaire (BRAESTRUP & MOONEY 1958, DU SAULT 1959, LEGARE 1964a) sont presque identiques pour les mannequins semi infinis et infinis Dans le présent travail, on a trouvé que l'on peut aussi tracer d avance les isodoses des champs obliques simples ou multiples Les seuls écarts d isodoses entre les deux sortes de fantome se trouvent aux 3 a 4 premiers centimetres de tissu, cet écart diminue a mesure que le champ diminue de taille

La fraction de temps $\theta/180° = 2\theta/360°$, durant laquelle un point est irradié, est un facteur géométrique independant du tissu (Fig 3)

Les isodoses (Fig 4a) issues sont independantes de la DPC pourvu que la DSC demeure constante (60 cm ici) Les centimetres de tissu le long de l axe central entre son point d entree et le centre de rotation ne servent qu à ajuster le temps d exposition pour exposer le centre de rotation a 100 R Ceci s obtient

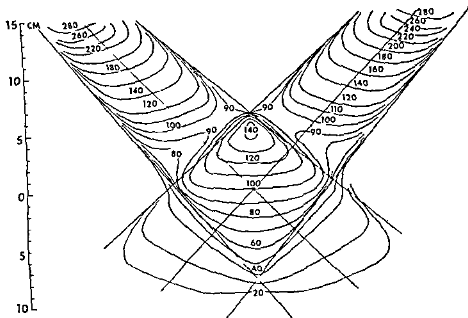


Fig 9 Isodoses préalables de deux champs obl ques (DSC = 60 cm α = 45 d am = 10 cm)

à partir du taux (R/mn) dans l air et du rapport T/A pour cette distance D sur l axe central et pour le champ au centre de rotation

La figure 7b illustre l avantage dosimetrique de la double couronne sur les isodoses provenant de deux champ en sens inverse (Fig 7a) La dose est plus faible à la p au et au tissu sous cutané parce qu en therapie en couronne ces tissus sup rficiels ne sont exposes que pour un instant a chaque rotation

Comme on le verra les isodoses telles qu obtenues par cette methode ne sont pas de haute precision Pour obtenir les isodoses reelles on doit se servir de la methode amélioree qui suit

Therapie en couronne (*methode ameliorée*) Tout comme dans la methode simplifiee les isodoses sont calculées au préalable (Tableau B) et s appliquent donc à toutes les épaisseurs de tissu Il suffit de sup rposer la coupe du patient sur les isodoses obtenues Ceci s applique aussi bien a la couronne simple (Fig 6) qu a la double couronne (Fig 8)

La couronne simple (Fig 6), contrairement a deux champs obliques (Fig 9) ayant le meme angle α a la face d entrée permet d exposer les premiers centimetres de tissu a un faible niveau tout en donnant une dose tumorale voulue

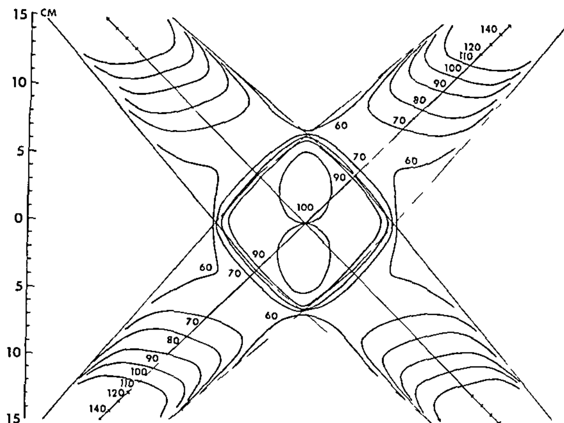


Fig 10 Isodoses préalables de quatre champs obliques (DSC = 60 cm a = 45 diam = 10 cm)

La couronne double (Fig 8) permet d obtenir une excellente distribution tumorale et ceci en ne cédant que 20 % a 10 % de cette dose a la peau Cette distribution est symetrique a l'axe de rotation Cette distribution par thérapie en couronne est nettement supérieure a la distribution issue de deux champs en sens inverse (Fig 7a) a quatre champs (Fig 10), ou a la cyclotherapie (Castro & Whitcomb 1963)

Discussion

L'emploi de la cyclotherapie en couronne, technique d exécution simple, est justifiée du point de vue dosimétrique par la haute valeur qu elle presente pour la relation *dose profonde/dose superficielle* Ceci se voit assez bien en comparant les isodoses de la cyclothérapie en couronne a celles des autres techniques de champs fixes ou cinétiques

La difficulté d'obtenir les courbes d isodoses pour la télécobalt thérapie en couronne est contournée, et pour la methode simplifiée et pour la méthode

amehoree De plus ces isodoses préalablement calculees pour un angle α constant et un champ donne a une DSC fixe sont les memes d une sorte d appa reil a un autre pourvu qu il n y ait pas trop d écart de dose dans la penombre du champ oblique immobile Les appareils fonctionnant a une DSC plus grande que 60 cm cedent une dose cutanée et sous cutanée inferieure a celle donnée dans ce travail

La methode de calculs prealables peut s appliquer aux appareils de cobalt 60 ainsi qu aux machines à rayons roentgen de haute energie (WHEATLEY et coll 1953, JENNINGS & McCREA 1957) La méthode ne peut toutefois pas s appliquer aux machines a rayons roentgen d énergie moyenne (GREEN et coll 1949 MARQUES & CANIHAC 1950 QUIMBY et coll 1954 NORIEGA LIMON & AGUILAR 1955 MARQUES et coll 1958)

En comparant les isodoses de la méthode simplifiée a celles de la méthode amehoree on voit que la derniere méthode est beaucoup plus precise

Remerciements

Nous tenons à remercier le Ministère de l Education du Québec de la Bourse de Perfectionnement accordée à l un de nous (J M L) au cours de ces travaux

RESUMÉ

Les auteurs ont établi a l avance par calcul les isodoses pour la télécobalt thérapie en couronne et pour des champs obliques On obtient une distribution de dose optimale par simple déplacement de la coupe du malade sur les isodoses L irradiation en couronne simple donne une meilleure distribution de dose que deux champs obliques ayant le même angle d incidence L irradiation en double couronne donne une excellente distribution a la tumeur et une faible dose (20 a 40) cutanée et sous-cutanée supérieure à l irradiation par champs multiples ou rotatoire

SUMMARY

I recalculated dose distributions have been obtained for crown and obl que beam cobalt 60 teletherapy Optimum distribution can be had by simply shifting the patient s cross-section over the isodose distribution Comparison between various treatment plans shows that the simple crown technique gives better dose distribution than two oblique fields with the same angle of incidence Because of its excellent tumor dose distribution and low (20 to 40) skin and subcutaneous dose the double-crown technique is usually superior to multiple field and rotation therapy

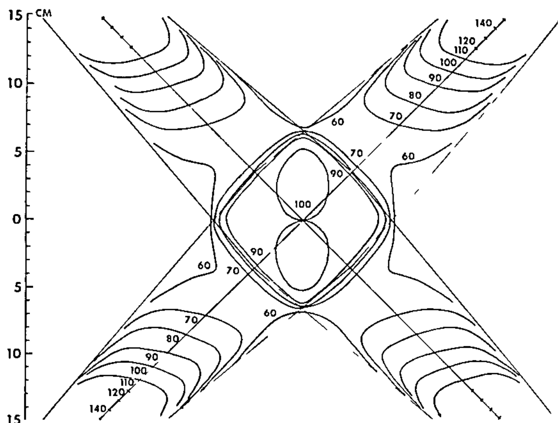


Fig 10 Isodoses préalables de quatre champs obliques (DSC = 60 cm α = 45 diam = 10 cm)

La couronne double (Fig 8) permet d obtenir une excellente distribution tumorale et ceci en ne cédant que 20 % a 40 % de cette dose a la peau Cette distribution est symétrique a l'axe de rotation Cette distribution par thérapie en couronne est nettement superieure a la distribution issue de deux champs en sens inverse (Fig 7a) a quatre champs (Fig 10), ou a la cyclothérapie (CASTRO & WHITCOMB 1963)

Discussion

L'emploi de la cyclothérapie en couronne technique d execution simple, est justifiee du point de vue dosimetrique par la haute valeur qu elle présente pour la relation dose profonde/dose superficielle Ceci se voit assez bien en comparant les isodoses de la cyclothérapie en couronne a celles des autres techniques de champs fixes ou cinétiques

La difficulté d obtenir les courbes d isodoses pour la télécobalt thérapie en couronne est contournee, et pour la methode simplifiee, et pour la methode

Book reviews

PROTECTION OF THE PUBLIC IN THE EVENT OF RADIATION ACCIDENTS Proceedings of a Seminar jointly sponsored by the Food and Agriculture Organization of the United Nations by IAEA and by the World Health Organization 370 pages WHO Geneva 1965 Price 37 shillings 6 pence

The problems defined in the title are viewed from many different aspects by a group of experts convened at Geneva in November 1963 by the organizations mentioned Only hazards to the general public and not those to radiation workers were considered

In a general medical introduction the attention is drawn among other things to the necessity of balancing the hazards to the population if nothing were done after a serious radiation accident against the risks that counter measures in themselves might create a point that recurs in several other passages in the book A subsequent section provides a general review of the various types of radiation accidents of public concern that may occur and towards which action should be taken immediately and after that a summary of the observations made has led to a clear view of the situation Thereafter the meteorologic factors that determine the spread of released radioactivity in the atmosphere as well as agricultural and other aspects on the movement of radioactivity in food chains are discussed Another series of papers deal with the assessment of the somatic and genetic hazards of radiation the uncertainty still prevailing in estimating the incidence and severity of the effects of small radiation doses is duly stressed

The need for preplanning is discussed in other papers in relation to any imaginable accident that may occur in a nuclear power plant so that relevant measurements can be made quickly and transformed into speedy and efficient but no too excessive counter measures It is important that this preplanning includes all authorities concerned that the plans are tested in practice and revised from time to time and that constant watchfulness is maintained even after many accident free years Consideration is given to the value of having previously fixed action levels for triggering various types of action as compared to a more flexible system with more regard taken to special circumstances in an individual case Public relations aspects are al o considered in several papers

The relative importance under varying conditions of certain radionuclides (the only important ones are usually those of strontium iodine and cesium) and of various modes of irradiation (from a passing radioactive cloud from depositions on the ground from inhaled radioactivity from various foodstuffs from drinking water and the like) is estimated Practical measures such as instructing people to stay indoors for a certain time or evacuation of people decontamination of foodstuffs and water as well as more long range work for reclaiming heavily contaminated land are discussed Measurement apparatus and methods are also discussed

Discussion reports presented after the various sessions increase the value of the book the acquisition of which may be regarded as essential to all who are responsible in achieving radiation safety such as physicians physicists technicians and civil service staff

Sten Benner

ZUSAMMENFASSUNG

Die Dosisverteilungen bei Kobalt 60 Bestrahlung wurden für Felder 'en couronne' und für *schräge Felder* vorausberechnet Die optimale Dosisverteilung wird dadurch bestimmt dass man den Querschnitt des Patienten im Verhältnis zu den Isodosen einfach verschiebt Bei Bestrahlung 'en couronne simple' erhält man eine bessere Dosisverteilung als bei Bestrahlung von zwei schrägen Feldern mit demselben Einfallswinkel Mit der Bestrahlungstechnik 'en couronne double' wird eine vorzügliche Tumordosis erzieht während die kutane und subkutane Dosis niedrig gehalten wird (20 bis 40 %) auf diesem Grund ist diese Technik derjenigen mit multiplen oder rotierenden Feldern vorzuziehen

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ROLF SIEVERT IN MEMORIAM

On the 3rd December 1966 the creative and powerful life of Professor Emeritu Rolf M Sievert was suddenly brought to an end at the age of seventy by a thrombosis a few days after a major surgical operation Thus ended an epoch in the Swedish and the international history of medical physics and radiation protection

Rolf Sievert was a pioneer in medical radiation physics and continued until his unexpected death with his energetic and inspiring work in this field This started almost fifty years ago when he offered the radiologists at Radiumhemmet the benefit of voluntary and unpaid collaboration After a few years a physical laboratory was created at the clinic and Sievert was appointed its head The laboratory developed under his leadership to an internationally well known research institute and in 1938 the newly built Institute of Radiophysics at the Karolinska Sjukhuset was opened In 1941 a professorship in radiation physics was established at the medical faculty and Sievert appointed its first holder

The clinical application of radiation physics was a main interest for Sievert throughout his whole life although his own main inventions and contributions in this field were made b fore 1940 Through the fundamental work on dose determination of radium sources he received the honour of being eponymous to a mathematical expression the Sievert integral Sievert and his collaborators investigated at an early stage the secondary radiation from various materials and

ACCURACY IN MEASUREMENTS AND CALIBRATIONS 1965 Technical Note 262 Ed by W A Wildhack R C Powell and H L Mason 145 pages, 66 diagrams National Bureau of Standards U S Department of Commerce Washington 1965 Price 1 00 dollar

The charts that constitute the main part of this book indicate the present relative uncertainty in the measurement of various physical quantities at the NBS and the increased accuracy aimed at during the next five years In many cases the accuracy with which instruments can at present be calibrated at the NBS and other laboratories is given and the charts are followed by general comments on such as measurement methods state of the art, and industry s needs

Physicists concerned with radiology will find useful data on the measurement of such quantities as roentgen ray energy exposure and electron beam current and also on electrical measurements

Sten Benner

CURRENT TOPICS IN RADIATION RESEARCH Vol 1 Edit by M Ebert and A Howard 272 pages 7 figures and 9 tables North Holland Publishing Comp Amsterdam 1965 Price 30 guilders

The volume contains six contributions by experts selected for their particular field of research It may be said at once that they have produced an excellent book

The first steps of the radiation action on living materia are initiated by the formation of free radicals which can be studied by electron spin resonance measurements i e a method of spectrometry using electromagnetic centimeter waves Too much work has doubtless been published in this field with but little heed to biologic observations so that the balanced article of ZIMMER & MULLER on the usefulness as well as the limitations of the method makes most satisfactory reading Radiation protection by chemical substances continues to be in the foreground of interest The understanding of the mechanism is helped by studies on simple chemical systems in which the interaction between protective substances and the radicals give better evidence than analyses of biologic material of complex structure Some simple bacteriophages have however proved to be useful for in vivo studies and NAKKEN has provided up to date information on this basic subject Bioamines especially serotonin has been proved to afford good radiation protection one of the leading experts in this field MELCHING deals excellently with the matter

The bone marrow cells and particularly the so called stem cells from which by division the peripheral blood cells are produced rank among the most radiation sensitive mammalian cells Little has been known so far about the kinetics of the radiation effect on this system LAJTHA and his associates have brought much new evidence into this important field with its many practical implications

Renewed interest in fractionated dose irradiation has been awakened following ELKIND S beautiful work on cultured mammalian cells A recovery of cell damage occurs after sublethal doses and a second dose at variable times after the first one produces complex survival curves The further studies of the fractionation technic may possibly be of importance in radiotherapy of malignant growths The last article by STEWART & HEWITT on the incidence of leukemia in children caused by radiation exposure in early or even prenatal life is a well conceived and documented appraisal of our present knowledge This is probably the section that will offer radiologists the most valuable practical information

Arne Forssberg

FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR PROF K LIDÉN), UNIVERSITY OF LUND, SWEDEN

TIME VARIATION OF CESIUM 137 AND POTASSIUM IN HUMANS FROM SOUTHERN SWEDEN

by

L G BENGTSSON

This paper deals with investigations of fall-out ^{137}Cs and natural potassium burdens in people from Southern Sweden Two main groups were measured three times a year from the beginning of 1964 through 1966 One group comprised 13—15 year old school children from Lund and the other one adults working at a large factory at Lund Originally all members of both groups lived in the city of Lund or close to it In 1966, some migration had occurred to villages within a distance of 20 km from Lund

From the beginning much effort was made to keep the groups intact and one way of doing this was via information Every subject was given introductory articles explaining the meaning of the measurements and some fundamentals concerning radioactivity and radiation The result of the measurement of the individual was reported to him from time to time The adult group has appreciated these efforts and all members of the group are willing to take part in future measurements The other way of keeping the groups intact was our close contact with them Anybody who did not appear at the agreed time of measurement was asked by telephone to come some other time With

Submitted for publication 27 February 1967

pointed out its importance, both in medical applications and with respect to radiation protection considerations. He designed several teleradium units and developed methods to improve radiation protection in their medical use. His most important inventions were probably the numerous types of ionization chambers for basic research, clinical dose measurements and radiation protection surveys as well as personnel dosimetry. The most well known type is usually referred to in the literature as the Sievert chamber.

Sievert soon realized the importance of knowing more about the possible biologic significance of natural radiation. He started environmental radiation measurements and radiobiologic investigations at low dose levels as early as in the 1930's and became in the late 1940's a pioneer in measurements of the gamma radiation from the human body with pressure ionization chambers.

In 1925 Sievert designed suitable equipment for a mobile group for the inspection of roentgen departments at hospitals all over Sweden and started examination of their radiation sources. This activity grew rapidly and with the first Swedish radiation protection law in 1941 the Institute of Radiophysics became responsible for licensing and inspecting all the medical and industrial uses of ionizing radiation. The increased employment of roentgen rays and radioactive substances in the twenty years that followed required continuous expansion of the supervision work. In 1965, reorganization became necessary and, as his last great achievement before he retired, Sievert organized the present National Institute of Radiation Protection.

Sievert was a member of the International Commissions on Radiological Units and Measurements and on Radiological Protection (ICRU and ICRP) from their creation in 1928 and chairman of the latter during the years 1956—1962. Sievert took an active part in the establishment and organization of the United Nations Scientific Committee on the Effects of Atomic Radiation and was its chairman during the years 1958—1960. He initiated the Nordic Radiation Protection Association which was founded in 1964 and became its first chairman. Due to the great respect won by his work in these fields Sievert received many national and international honours and had the privilege of receiving frequent tokens of respect and friendship. His enthusiasm and imagination reached outside his main field of interest. During the Second World War he initiated physical research for the national defence in Sweden and became the leading instigator in establishing the Geophysical Laboratory in Kiruna, in the far north of the country.

Sievert's enormous working capacity, his profusion of imagination and his never failing interest, even in minor projects, made his leadership a challenge to all members of his staff. The most characteristic feature of Rolf Sievert in person was the stamp of generosity he bore, not only in entertaining his guests, but also in tolerance and understanding. He was always prepared to share both his valuable time and his private resources to help and encourage his closest friends as well as any individual in his neighbourhood.

Rune Walstam

Methods The subgrouping and the average ages and weights of the groups are given in Table 1 together with the minimum and maximum ages and the estimated standard deviation (SD) of the weights These groups were measured in February, June and September from 1964 to 1966 (boys and girls left school in June 1966 and did not take part in the September 1966 measurement) Whole body counting during 30 min was performed in our steel room using chair geometry and a 8 × 4 crystal (for details about counting geometries and equipment see ref 'Directory of whole body radioactivity monitors 1964) The pulses were analysed by a RIDL 200 channel analyser model 34/8 and pulse height spectra were punched on paper tape Cesium and potassium contents were calculated on the SMIL computer at Lund which was also used for other calculations

In 28 of 485 measurements the 45/144 cm scanning bed geometry was used (February 1964 and June 1966) This caused unnecessary uncertainty because the sensitivity for one particular individual reproduces better if only one geometry is used From the potassium measurements, indications were found that the change from chair to scanning bed geometry in some cases influenced the group averages by a few per cent and also caused increased spread of the values within the group The ^{137}Cs values ought to have been influenced in about the same way The effects are however so small and concern such a limited number of measurements that they very little affect the general results

All subjects had a shower and hair wash before the measurement They wore cotton overalls the radioactivity of which was checked at irregular intervals Background studies were made with a 65 kg non active sugar phantom in place of the subjects

Evaluation of results The results were evaluated in two different ways First the averages of body weight potassium content (gram K) potassium concentration (gram K/kg body weight) cesium content (nCi ^{137}Cs) cesium concentration (nCi ^{137}Cs/kg body weight) and cesium/potassium ratio (pCi ^{137}Cs/gram K) were calculated for all groups and thus the absolute levels and their variation with time were found The standard deviation (SD) for all quantities were estimated for each group in order to give an estimation of the spread of the quantities in the populations from which the groups were sampled The standard errors of the mean values (SE) were also estimated in order to provide an estimate of how well the mean values for these very groups were representative of those of the population It should be observed that since the composition of the groups did not change with time the measurements after February 1964 gave only little additional information for the estimation of the population values from the group values For instance if the true

Table 1

*Age weight and potassium data for the groups Data for weight and potassium give the averages over the period 1964—1966 Figures marked with * were not constant during that period SD = standard deviation SE = standard error of the mean value*

Group	No	Age on 7 February 1964 a		Weight kg		Potassium content g		Potassium concentration g/kg body weight	
		Average	(Min max)	Average	SD	Average	SE	Average	SE
Boys	11	13 6	(13 1—14 1)	55*	8	110*	6	2 04	0 07
Men 1	8	33 1	(30 7—34 2)	72	9	143	5	2 01	0 06
Men 2	10	49 0	(44 2—53 7)	80	11	144	6	1 82	0 05
Girls	17	13 8	(13 3—14 2)	51*	7	87	2	1 72*	0 04
Women 1	5	25 2	(19 0—31 7)	55	12	90	4	1 65	0 10
Women 2	6	39 7	(34 1—43 0)	61	10	93	3	1 55	0 06

these precautions, the only lost chances of measurement were due to the subjects having quitted the Lund area Only subjects measured at all occasions were included in the study (from these subjects two measurements out of 485 were lost and the corresponding results were assumed to be the average of the results before and after the lost measurement) The subjects ultimately lost represented none of the extreme cesium or potassium contents within their groups at the times they were measured Of 33 school children, 28 attended all measurements The corresponding figures for adults were 34 and 29

All people working at the great factory were asked if they wanted to participate in the measurements Almost all women that answered positively were included in the control group From the men the positive answers were so many that it was possible to select two groups of rather narrow age ranges These groups were chosen to include about one half of blue collar workers and one half of white collar workers

The school children on the whole belonged to the same class since they started in the first class This was recruited from the population in a given geographic area, as representative as possible of the southern Swedish urban population Most of the adults in this area are labourers but quite many are office workers, nurses, and the like, whereas few are farmers, higher officials, or university graduates The school children in this study have parents with occupations that reflect the general pattern for the area considered

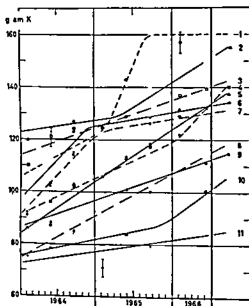


Fig 2 Individual variation of body potassium with time in boys The 11 individual curves were fitted by eye to the measured points The right hand side of the figure (after June 1966) was only added for ease of identification of curves and signs and those signs do not represent measurements Bars on some points indicate ± 1 SD from the counting statistics of the measurement

patterns normalised in a similar way As will be shown later it was also possible to make use of the information given by the standard deviation (SD) of the normalised potassium content at a given time for groups whose potassium content was essentially constant with time

Results

1 General The relative (or fractional) standard deviation from counting statistics for an observed amount of ^{137}Cs and potassium is given in Fig 1 For potassium this statistical error contributes substantially to the uncertainty of some of the performed analyses

A systematic yearly weight variation with time exceeding 1 % was only found for boys and girls For the other groups the deviations from the averages given in Table 1 seemed to be at random and were usually smaller than ± 1 % For boys and girls the weight increased approximately linearly with time at a yearly rate of 12 % for boys and 5 % for girls

2 Potassium The individual results for boys are given in Fig 2 A variety of patterns emerge and it is evident that much information is concealed when only the mean values for the group are used

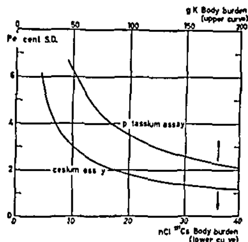


Fig 1 Relative standard deviations of result from measurements of cesium (lower curve and lower scale) and potassium (upper curve and upper scale) contents of a single individual The statistical error *in the ^{137}Cs analysis is only slightly influenced by* the amount of potassium present

population value were 10 % higher than the *corresponding group value in* February 1964, and if the time variation of the group quantity were the same as that of the population quantity, then the population value would still be 10 % higher than the group value in June 1966

The second way of evaluating the results was performed in order to assess as accurately as possible the time variation of the six quantities mentioned above As discussed above, once the spread of the individual values has been established, it is more interesting to study the time patterns and possible individual and group variations in these It seemed likely that the time patterns would be very much the same for individuals within the same group because (1) the groups were homogeneous with respect to sex and age (for instance the biologic half time for cesium depends on sex and age), (2) the groups contained no persons with extreme dietary habits, (3) the radioactivity intakes arose from several dietary items (and thus peculiarities from one given food item would be averaged out)

Therefore, a normalisation procedure was tried in which an individual's result at a certain time of measurement was divided by the average of his results from the eight first measurements This normalisation was undertaken for all the six quantities mentioned above, with the result that the variation with time of these quantities falls around 1 for each individual This makes possible an estimation of the significance of time pattern differences between the populations represented by the groups The estimation was made in the following way The standard error of the mean value of the normalised quantity (SE) was estimated for each group This SE was assumed to give, as usual, confidence intervals for the population value of the normalised quantity For the cesium concentration and the cesium/potassium ratio the normalised time patterns were used for comparison *with theoretically calculated time*

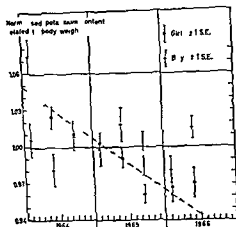


Fig 3 Variation of normalised body potassium concentration (g K/kg) with time in boys and girls Their average age was about 13 5 years at the beginning of 1964 The dashed line gives a regression line of the potassium concentration of girls versus time fitted by eye

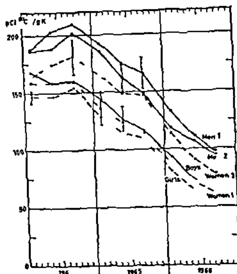


Fig 4 Average variation of cesium/potassium ratio (pCi ¹³⁷Cs/g K) with time in the investigated groups Bars give one standard error of the mean value of the ¹³⁷Cs levels for the time variations other limits of error apply (cf fig 6)

tive standard deviation was approximately 25 % for all groups For the female groups no representation gave significantly smaller spread than any other For males the relative standard deviations within the populations were estimated to about 30 % for the cesium content about 25 % for the cesium concentration and slightly above 20 % for the cesium/potassium ratio

From the normalised curves for the cesium content it should be possible to state whether the observed time patterns for the groups are significantly different In Fig 5 the normalised ¹³⁷Cs contents for boys girls and men the last group comprising both men 1 and men 2 are given (Any differences are so small that the results for men 1 are not significantly different from those of men 2, and the same holds for women 1 and women 2, but if the joint groups men 1 and men 2 called men and women 1 and women 2 called women are studied some significant results emerge) The curves for boys and girls represent the limits of the time variations and the curves for men and women fall between them women following closely the pattern for men

The ¹³⁷Cs content in boys decreases significantly slower than for girls which may well be caused by the larger weight increase in boys There is also some tendency for the cesium content of girls to decrease more rapidly

In the other groups, the individual potassium values do not vary much with time, and the mean values can be used with more confidence

The average potassium contents over the time period considered for the various groups are given in Table 1 The potassium content changed with time only for boys, in whom it increased yearly by 13 % Any decrease for men-1, men-2, women-1 and women-2 would be less than approximately 2 % per year, any increase for girls would also be less than approximately 1 % per year (at the 95 % confidence level)

Since the weight and the potassium content increased in about the same proportion for boys, the potassium concentration was constant, as is apparent from Fig 3 The normalisation was used in order to obtain the limits of error A positive or negative slope of 2 % per year is not consistent with the experimental points ($p < 0.02$ according to the chi square test (NATRELLA 1963)) It is important to note that a correction has been applied to the results because of the varying sensitivity of the chair geometry for subjects of varying weight This correction amounted to 0 3 % per kg body weight (sensitivity is smaller for higher weights) For girls, the yearly decrease was 4 %, for the other groups there might be a decrease of about 1 % per year

For the potassium concentration the estimated standard deviation within each group was 8 to 13 %, and the same was the case with the potassium content, except for boys, in whom the standard deviation was 19 %

3 Cesium 137 From the study of the ^{137}Cs content of members of a given group it was found that some individual variations in the time pattern do occur For instance some individuals had their maximum value during June 1964, while others had theirs in September 1964 The variations are, however, relatively small

The cesium/potassium ratios for the various groups are given in Fig 4 The bars give the estimated standard error of the mean values of the groups Men 1 and men 2 have, in fact cesium contents about twice those of the other groups, but if the body burden of ^{137}Cs is divided by the body potassium content, the groups fall closer to each other, as may be seen from Fig 4 For the cesium concentration the results are similar to those for the cesium/potassium ratio

In the three ^{137}Cs representations, men 1 have the highest values and girls the lowest As to the cesium content, cesium concentration and cesium/potassium ratio, the values for girls in per cent of those for men 1 varied from 48 to 35, from 73 to 47 and from 77 to 58, respectively

The estimated standard deviations for the populations represented by the groups were studied with respect to the three ^{137}Cs representations The rela

Table 2

Model used for calculation of dietary intake of ^{137}Cs from various food items based only upon the measured ^{137}Cs content of milk

Percentage of total dietary intake*	Food component	Correlation to milk activity
0 48 R	Milk ice cream	Proportional
0 32 R	Beef beef products dried milk cheese	Proportional to that of preceding month
20	Pork pork products fish coffee tea	Proportional to that of preceding 12 month period
0 80 (100 R)	Cereals vegetables fruits and berries	Proportional to that of the 12 month period preceding harvest Delayed consumption

For the hypothetical case that the milk activity has been constant for a long time

girls Unfortunately the groups are too small and the errors become too large for any conclusions about differences The results nevertheless give a clear hint that the curve for normalised cesium/potassium ratio for girls follows that for boys (which is almost the same as the curve for cesium concentration in boys) while the curve for normalised cesium concentration in girls decreases faster than the curves for boys

Finally the standard errors for the points of the normalised curve are not significantly influenced by the representation chosen cesium content, cesium concentration or cesium/potassium ratio

Body burden variation with time derived from dietary ^{137}Cs data

Only a very simple form of dietary investigation was made for the groups studied The subjects were asked to state their consumption of various dietary items as none or below equal to or above average This investigation could only be used to find out dietary habits towards one extreme or the other Further no detailed measurements of the radioactivity content of other food stuffs than milk were available

Still some interesting results can be obtained by using only the data for the ^{137}Cs content of milk LINDELL & MAGI (1965) found a good correlation between the ^{137}Cs concentration in beef during one month and that of milk during the preceding month There is further good correlation between the ^{137}Cs concentration in pork and that in milk during the preceding 12 month period Finally milk milk products meat and meat products are responsible for the major part of the food intake of ^{137}Cs Their shares can be estimated from data in the United Nations 1966 Report Since there should be a delay between the appearance of ^{137}Cs in milk and meat on one hand and in cereals and vegetables on the other the relative contribution of milk and meat to the dietary ^{137}Cs intake is best estimated from the values found in years when the fallout level has been approximately stable for some years From this point of view 1964 or 1965 would be suitable years In 1964 milk and meat and

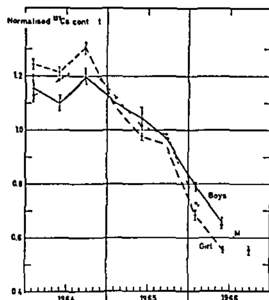


Fig 5 Average variation of normalised (see Evaluation of results) ^{137}Cs body burden (nCi ^{137}Cs) with time for groups of men boys and girls Bars give ± 1 standard error of the mean value of the normalised ^{137}Cs level The curve for women falls approximately between those for men and girls

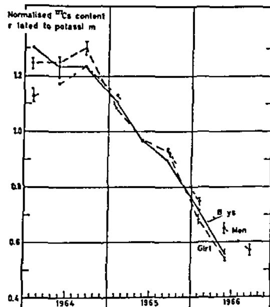


Fig 6 Average variation of normalised cesium/potassium ratio (pCi ^{137}Cs/g K) with time for groups of men boys and girls Bars give ± 1 standard error of the mean value of the normalised cesium/potassium ratio The curve for women falls approximately between those for men and girls

than in men and (not shown in the figure) for the curve representing women 2 *to follow that representing men, while the curve for women 1 follows that* for girls The last fact may be caused by the composition of the group of women 1, which comprised several rather young women

More interesting results come from the study of the cesium content as related to body potassium or body weight The normalised curves for the cesium/potassium ratio for men, boys and girls are recorded in Fig 6 The difference between boys and girls that may be observed in Fig 5 has almost completely disappeared but men reach their maximum later than boys and *girls and the decrease is slower Women fall between men and* boys girls, there is again a tendency (not shown) for the curve of women 1 to follow girls, and for the curve of women 2 to follow men (Men 1 and men 2 follow each other closely)

Approximately the same results come out if the normalised curves for the cesium concentration are studied For boys, the normalised curves for cesium as related to body weight and to body potassium follow each other very closely Since the girls increased in weight but had constant potassium content, there *is an interesting* possibility to compare the time variation for boys and

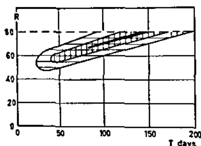


Fig 8 Connexion according to experimental data for men between the parameter R (percentage of the joint radioactivity intake from milk beef and cereals that originates from milk and beef see Table 2) and the biologic half time T in the model used for calculation of the curve of body content of Cs versus time The black area indicates values of R and T that give a calculated curve which falls within the experimental points ± 2 SE for 7 or more of the 9 points the cross hatched area corresponding to 5 or more and the area with lines to 3 or more The experimental points are taken from the normalised curves of cesium/potassium ratio for men

for which the effective half time will certainly be between 25 and 200 days for the groups in this study In the calculation the remaining 10 % are assumed to be immediately excreted (the half time is 1 to 2 days)

The two parameters T (half time) and R have some connection For small values of R the ^{137}Cs intake is changed towards an intake with the activity much delayed compared to the milk activity and thus a small value of R is expected to serve to smooth out the curve for variation of body burden with time A similar effect is expected if a large value of T is chosen

For the given values of the two parameters (25 d < T < 200 d and 25 < R < 75) the curves for variation of body burden with time were calculated using monthly averages for the ^{137}Cs content of milk measured mainly at the Institute of Radiophysics Stockholm (LINDELL ÅBERG FREDRIKSSON and EDVARDSON 196? SVEDJEMARK 1966) For comparison with the experimental results the calculated curves for body burdens were normalised with a procedure similar to that used for the experimental ones

An example of the results is given in Fig 7 The curve for R = 70 T = 100 d provides a reasonable fit to the experimental points for the normalised cesium/potassium ratio for men while the curves for R = 60 T = 100 d or R = 70 T = 50 d hardly are acceptable By using several such theoretical curves a set of values for R and T could be selected that gave an acceptable fit An example of the distribution of such values is presented in Fig 8 from which may be seen that R and T as expected work in opposite directions so that a large value of R must be paired with a large value of T if a good fit to the experimental results is to be obtained It should be noted that these values of R and T have been deduced *only from* the shape of the experimental curves So far the total intake and body burden of ^{137}Cs have not been used

A special problem relates to the varying biologic half time in growing children LIDEN (1964) and MC CRAW (1965) have reviewed ^{137}Cs metabolism and found that the half time for the slow component increases from about 20 days at birth to roughly 100 days at 20 years Assuming a linear increase in the half time of 4 days/year the biologic half time for the school children studied would have undergone a change by 10 d during this study For R = 70

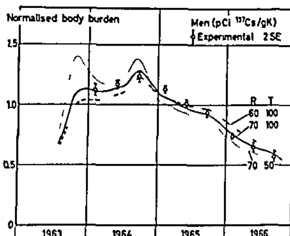


Fig 7 Calculated curves for the variation of normalised body ^{137}Cs with time for some values of the parameter R (see Table 2) and the biologic half time T Experimental points give normalised cesium/potassium ratio for men ± 2 SE

products derived from them contributed the following percentages of the total dietary intakes Chicago in USA 56 % United Kingdom 78 % Germany 66 % Denmark 45 % Sweden 63 % It may then be reasonable to assume that for the groups in this study milk and meat and their products contribute 60 ± 20 % to the total dietary ^{137}Cs intake provided the fall out rate has been constant for some years The limits of error have been chosen quite large because the dietary habits of boys and girls may be different from those of adults According to LINDELL & MAGI the contribution from pork should be about 15 % Based upon this information the model given in Table 2 was used to calculate the dietary intake of ^{137}Cs using only the ^{137}Cs content of milk The parameter R gives the percentage of the joint radioactivity intake (excluding the pork group) originating from milk milk products beef and beef products For cereals and the like there is a delay between production and consumption It has been assumed in the calculation that the harvest of these products has been at the end of August each year and then that 1/12th of the consumption in September comes from the new harvest and 11/12ths from that of the preceding year In October the corresponding figures have been taken to be 2/12ths and 10/12ths and so on Application of this model to Danish data (AARKROG LIPPERT & PEDERSEN 1963 AARKROG & LIPPERT 1964 1965 1966) predicted levels in wheat flour within a factor of 2 for the period 1962—1965 and gave somewhat poorer prediction for rye flour It is difficult to obtain a better prediction with simple models because (1) the correlation between grain activity at harvest and milk activity is very uncertain (2) there is a delay of up to some months before the mills start working with the new harvest (3) the flour marketed in Southern Sweden is mixed with 10 to 30 % foreign flour (4) it is also mixed with flour from previous harvests and (5) flour produced one year is partly stored and may be marketed one or two years later

Since cereals should contribute 40 ± 20 % of the dietary ^{137}Cs intake (fish coffee and tea should give 2 to 5 % and are neglected in this estimation) R (see Table 2) should be 50 ± 25 if the assumption regarding the correlation between the flour and the milk ^{137}Cs concentrations is correct

In order to find the body burden one must also assume a retention model for ^{137}Cs It is known that a two exponential model well covers most retention curves studied hitherto as was reviewed by LIDÉN (1964) *For the study of the long term retention* the most important parameter is the slow excretion which occurs for about 90 % of the ingested activity and

Table 3

Comparison of the assumed relative calori consumption and the estimated relative dietary radioactivity intakes for the investigated groups — The corresponding figure for the Swedish population as a whole is 1 00

	Men	Women	Boys	Girls	Weighting factor
*Calori consumption**	1 30	0 82	1 27	0 98	
Calori consumption from Swedish data	1 23	0 76	1 23	0 90	
Fluid milk***	0 82	0 59	1 70	1 13	0 8
Slices of meat*	1 38	1 00	1 13	0 80	1 0
Slices of white bread *	1 23	0 81	1 50	0 96	1 0
Weighted relative dietary Cs intake	1 16	0 81	1 43	0 96	

From the Food and Agriculture Organisation Calori requirements (1957)
From Abramson (1967)
* From the Bureau of the Census Consumption of selected food items in U S households (1963)

believed that about 95 of the results would fall within the range given by an estimation of the kind we have used (Compare the statement made by the Food and Agriculture Organisation A range of daily expenditure requiring between 2 400 and 4 000 calories for men and between 1 600 and 3 000 calories for women would appear to include most human beings — The limits are then ± 25 % from the average) The figures are in general agreement with what can be deduced from recent Swedish dietary investigations (ABRAMSON 1967) The latter figures are also given in Table 3

For the calculations we assume further that the radioactivity intake is proportional to the calori consumption This would be true if the dietary composition were the same for all levels of calori consumption and it is evident that some departure from this situation exists An estimation of the possible error can be made from data obtained by the Bureau of the Census in the USA (Consumption of selected food items in USA households 1963) They report age and sex distributions of results from interview investigations of the at home consumptions of pounds of fluid milk slices of white bread and slices of meat

Assuming (1) that the relative consumption for the various U S groups also applies to Swedish groups (2) that the consumption of the three items studied is representative for the consumption of milk and milk products meat and meat products and cereals respectively and applying Swedish data for food radioactivity we find the relative radioactivity intakes for men women boys and girls given in Table 3 Certainly assumptions (1) and (2) are both crude approximations but from this estimation one might nevertheless conclude that it does not appear unreasonable that the intervals given by the calori consumption figures with the specified limits of error could cover the true values of the relative radioactivity intakes It may also be observed that in Table 3 the consumption corresponding to cereals (white bread) is very close to the weighted average dietary ¹³ Cs intake The deviations from the pattern of average dietary intake occur mainly for milk and meat but the time variations of the

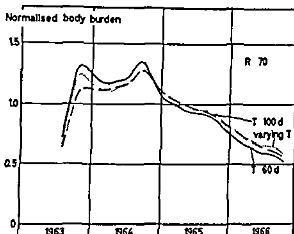


Fig 9 Calculated influence of variation of half time with age on the time variation of body ^{137}Cs The dotted curve results if T increases with age by 4 days per year of age when the half time on the average is 60 days during the period January 1964 to June 1966 About the same curve is obtained for fixed $T = 60$ d if $R = 60$

the curve for the time variation of ^{137}Cs, using $T = 60$ d, has been compared to a curve where the half time on 1 January 1964 was $T = 55$ d, and then increased by 4 d a year, as may be seen in Fig 9 The differences between the two curves have some similarity to the differences between the curves for $T = 60$ d and $T = 100$ d, and (not shown in the figure) about the same differences also exist between the curve for $R = 70$, $T = 60$ d, and that for $R = 80$, varying T The values of T, predicted for children merely from the shape of their curve of body burden variation with time, assuming a constant biologic half time, may thus be too high by 20 to 40 d, or the R values may be too small by 5 to 10 units (cf also Fig 8)

Further limits for R and T can be derived from the level of ^{137}Cs during the period considered In this case the model should allow for the dependence of the ^{137}Cs intake on sex physical activity age and body weight These parameters govern the calori intake and the dietary habits and among them the physical activity is usually difficult to assess In this study the physical activity is not under control in details and the best possible assumption is to consider the physical activity of the present groups as average The selection principles mentioned in the introduction ensure that at least the male groups are no extremes with respect to physical activity Of the women about half the number were engaged with work which they considered to involve an average amount of physical labour the other half considered their work as light Thus the average physical activity for women would probably not be at any extreme For boys and girls it is more difficult to assess the amount of physical activity However the way these children were selected gives no reason to believe that they should be much different from the average as far as physical activity is concerned

The relative calori consumptions for the groups as compared to the average for Swedes were estimated by use of the calori consumption figures given by the Food and Agriculture Organisation (1957) and are given in Table 3 It is estimated that the figures for the groups are correct to within $\pm$ 10 % in the sense that if the true calori consumption were studied for many groups using selection principles analogous to those employed in this study it is

Table 4

Measured values of the body burden of ^{137}Cs averaged over the period January 1964 to June 1966 and calculated half times (cf Fig 10) SE = standard error of the mean value

	Men	Women	Boys	Girls
Measured value	24 2	12 6	14 2	10 2
2 SE	3 2	1 9	3 4	0 9
Relative radioactiv ty intake	1 30	0 82	1 27	0 98
Measured value normalised to radioactivity intake 1 00	18 6	15 4	11 1	10 4
Calculated half time days	96	79	56	53
2 SE from measured body burdens days	13	12	10	5
Approximate error from radioactivity intake (2 SE) days	19	16	11	11

biologic half time (50 to 100 d)) The details of this estimation are given in Table 4 It results in half times of 100 ± 30 d for men, 80 ± 25 d for women 55 ± 20 d for boys and 55 ± 15 d for girls If the half time would vary line arly with age which is possible for boys and girls the same figures should apply to a good approximation if the given half time is taken to be that in the middle of the period of investigation

The half times and their limits can be used to find values of R from the relationships in Fig 8 and corresponding graphs for the other groups We find the R values for men to be 70 ± 5 for women 70 ± 10 for boys 70 ± 10 and for girls 60 ± 10 where the limits of error are such that one can guess that there is only 5 % chance that the true value would be found outside them The possible variation of half time with age for boys and girls could increase their R values by 5 to 10 units One should be careful in the inter pretation of the meaning of R values in terms of absolute radioactivity intake However they have in all likelihood a meaning for the relative radioactivity intakes of the groups The suggestion is ventured that no great differences exist in the composition of the diet of the different groups as far as the quickly varying component (including milk and meat) and the slowly varying com ponent (including cereals) are concerned This suggestion is at least not con tradictory to the results presented in Table 3 Because of the uncertainty as to the interpretation of the absolute value of R it is difficult to assess the cor rectness of the value R = 70 If the model is true this value would imply that 24 % of the radioactivity intake comes through food items the activity of which is proportional to the milk activity over a longer period of time and which are subject to a considerable delay between production and con

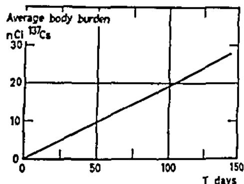


Fig 10 Dependence of the body burden of ^{137}Cs averaged over the period January 1964 to June 1966 on the assumed value of half time T for relative dietary radioactivity intake 1 00 The curve is valid to a very good approximation for $50 < R < 80$ For half times that vary with age the curve is also valid to a good approximation if T denotes the half time in the middle of the time interval (1 April 1965)

^{137}Cs levels of these food items follow each other quite closely The joint consumption of these two food items follows quite well *the average relative dietary ^{137}Cs intake*

The accuracy obtainable from equalling relative calori consumption and relative dietary ^{137}Cs intake can also be estimated in another way If the difference between the average calori consumption and that of the present groups were to be supplied from cereals (350 cal/100 g) from the average diet or from milk (60 cal/100 g) the relative radioactivity intakes would be 1 21 1 30 and 1 59 for men and 0 91 0 82 and 0 74 for women

For the absolute radioactivity intake the figures given by LINDELL (1964) are approximately consistent with those given by BLIX WRETLIND BERGSTROM & WESTIN (1965) for the food consumption per capita at the retail stage It is assumed in the calculations that fish and vegetables berries and fruits contribute 10 % in excess of the total radioactivity intake (in the equilibrium case) given by LINDELL and that 10 % losses originate from preparation of the food for consumption and waste at the household stage With these assumptions it is believed that the average radioactivity intake per capita is assessed correctly within ± 15 % the interval estimated to be a 95 % confidence interval Summing up all contributions to the error it seems reasonable to assume that the present estimation of radioactivity intakes for the groups using the mentioned absolute figures and relative calori consumption figures is in error by about ± 20 %, the given interval being a 95 % confidence interval

Using the thus derived figures for radioactivity intake we can apply the intake to our model and compare the calculated values with the measured The comparison is made using the body burdens for the groups averaged over the period February 1964 inclusive June 1966 When such a long time period is used, it is found from the calculations that the parameter R influences the calculated body burden only very little, so the resulting body burden is almost entirely dependent on the half time T This dependence is given for relative radioactivity intake 1 00 in Fig 10, where the body burden is the calculated average over the period January 1964 to June 1966 The measured body burden of ^{137}Cs and the estimated relative radioactivity intakes can now be used for estimation of the biologic half time T (the effect of the physical half life for ^{137}Cs (30 a) is negligible compared to that of the

Discussion

1 General At the Meeting in February 1966 of the Nordic Radiation Protection Society some details concerning the status of this investigation at the time were communicated by LIDÉN & GUSTAFSSON (1966) Since only two thirds of the measurements were done at that time, their report was incomplete and should be considered as replaced by the present communication

With regard to weight increase the groups of boys and girls behave as those in an earlier investigation of Swedish children from urban areas made by BROMAN DAHLBERG & LICHTENSTEIN (1942) The girls weighed about 2 kg less and the boys about 2 kg more than the standard weight Food habits for the adult and young groups may be less representative for people from the whole of Sweden than for those from Southern Sweden On the whole however some of the behaviour of the cesium and potassium in the groups should be representative for southern Swedes from urban areas and probably for southern Swedes in general apart from differences caused by local variations of the ^{137}Cs content of food For instance conclusions as to the metabolic rate for cesium and the individual spread of cesium and potassium values should probably be valid for much larger groups of Swedes than the limited groups investigated

2 Potassium. Potassium levels have been investigated for large populations by ANDERSON (1965) LORIMER et coll (1965) and by OBERHAUSEN & ONSTEAD (1965) The results of ANDERSON and of OBERHAUSEN & ONSTEAD for potassium concentration are shown in Fig 12, together with the results of the present investigation ($\pm$ 1 SE) There are no significant differences between the absolute levels of potassium concentration found in this investigation and those taken from the literature However, there seems to be one interesting detail to note about the observed time variation for boys and girls indicated by dotted lines From ANDERSON's results for boys of the corresponding age one can estimate the increase in potassium concentration with age to be 1 % to 3 % per year and LORIMER et coll give 2 % (according to their own drawing of the curve it is doubtful whether the data presented strongly support such an interpretation) The present investigation shows no such increase (less than 2 %) However the change in sensitivity of the whole body counter with increasing weight must be properly accounted for From data given by MILLER (1962) and by DELWAIDE & VERLY (1962) one can calculate a variation of sensitivity of chair geometries similar to ours amounting to 0 25 %/kg and 0 31 %/kg respectively These are close to our value of 0 32 %/kg If we assume that 0 25 %/kg would be a value more correct than

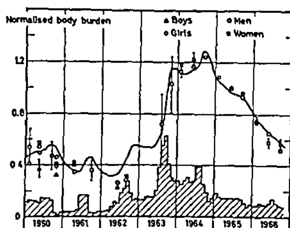


Fig 11 Predicted (solid line) and measured normalised cesium/potassium ratio (pCi ^{137}Cs/g K) Multiplication by 167 for men 138 for women 130 for boys and 118 for girls gives the absolute value of the measured concentrations As limits of error $\pm$ 2 SE are given The measured points 1960—1963 refer to heterogeneous groups and are not fully comparable to the points from 1964—1966 The filled bars give the used values of pCi ^{137}Cs/kg milk from 1960 to 1966 if the vertical scale is multiplied by 300

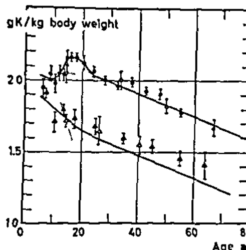


Fig 12 Potassium concentration from ANDERSON 1965 (filled signs) the present investigation $\pm$ 1 SE (open signs) and OBERHAUSEN & ONSTEAD (solid lines) Upper curve and rings refer to men lower curve and triangles to women The dotted curves for boys and girls indicate the trends of their potassium concentration variation with age For each group the value represents the average of the measurements from February 1964 to June 1966

sumption According to LINDELL (1964) there remain about 40 % of the radioactivity intake to be accounted for by such as cereals and fruits This need not be inconsistent with the actual 24 %, since these 40 % could be shared on slowly and quickly varying components

For R = 65, T = 80 d, the calculated curve for body cesium variation with time from 1960 through 1966 is given in Fig 11 The measured points for men and women during the period 1964—1966 are given and also some results from measurements of more heterogeneous groups during 1960—1963 The values for the cesium/potassium ratio have been used, and are divided for the 1960—1963 groups by the average values for the corresponding 1964—1966 groups The milk values from 1960—1966, used in the calculation, are also shown The uncertainty of the 1960—1963 measurements is large because of the varying composition of the groups and the small number of people in each group However, the results do not fit more badly to calculations than making it possible to state that the model used for the calculations may be suitable for describing the most important traits of the time variation of the body burden of ^{137}Cs

Discussion

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ours this would mean that the potassium concentration would have increased by 0.4 %/year more for boys and 0.2 %/year more for girls than was actually stated, since the boys increased in weight by about 6 kg/year and the girls by about 3 kg/year. The possible increase in the stated course of the curve of potassium concentration due to inaccurate correction for influence of body weight on sensitivity is not large enough to account for the apparent discrepancies found for boys, nor for those found for girls, as stated below. Redistribution of muscle mass might be another process influencing the sensitivity of the chair geometry. The effects are likely not to be large but they are difficult to estimate quantitatively. However, for boys a yearly increase of 1 % may be in accordance with the results of ANDERSON and of LORIMER et coll. and also with those of the present investigation. OBERHAUSEN, BURMEISTER & HUYCKE in 1965 presented a more detailed study of the potassium content in children and adolescents from 8 to 20 years, using part of the material presented by OBERHAUSEN & ONSTEAD. From their results one can calculate that the potassium concentration for 13 to 16 year old boys increases by 1 to 2 % yearly, and that of 13 to 16 year old girls decreases by 1 to 2 %. Thus, the results for boys in the present study need not be inconsistent with what has been reported in the literature. For girls, the decrease in potassium concentration with age is faster than reported by ANDERSON, and by OBERHAUSEN, BURMEISTER & HUYCKE, and the present data seem to be inconsistent with these. However, ANDERSON has pointed out that sampling errors may greatly influence the results, which is a consequence of the interrelationship between body potassium and muscle mass. This means that differences should exist in potassium concentration between groups with different body composition (caused for instance by different amounts of muscular work). Such differences have been found by LORIMER et coll. for large groups. ANDERSON, in a previous investigation, found for somewhat younger girls a very fast decrease in potassium concentration with age. More work is needed to establish whether these findings apply only to the special groups investigated, or to larger groups as well. It is of course possible that a similar situation exists also for boys so that the differences referred to earlier would be no matter of interpretation but real and due to the selection of the groups investigated.

The standard deviations of about 11 % for the potassium and potassium concentration values are in general agreement with those of about 12 % given by OBERHAUSEN & ONSTEAD and by ANDERSON. However, these authors do not mention such a large spread as the 19 % relative standard found in this study for the potassium content of 14 to 16 year old boys nor do OBERHAUSEN, BURMEISTER & HUYCKE. But from the detailed data given by the latter authors

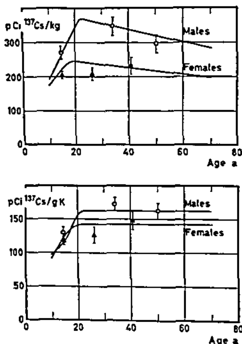


Fig 13 Levels of cesium concentration (upper figure) and cesium/potassium ratio (lower figure) The curves are from the figure given by OBERHAUSEN ONSTEAD & KEARY 1962 Their vertical scales have been multiplied by 2 in order to facilitate comparison with the present experimental results ($\pm$ 1 SE) which are given as rings for male and triangles for female groups For each group the values represent the average of the measurements from February 1964 to June 1966

it may be derived that for boys the relative standard deviation of the potassium content increases from about 14 % at 10 years to a maximum of about 19 % at 14 to 15 years and then decreases to about 13 % at 18 years of age (For girls the relative standard deviation is almost constant 14 to 15 % from 9 to 14 years whereafter it drops to 11 % at 20 years of age)

The standard deviations of the normalised potassium or potassium concentration values for men and women were on the average 3 6 % and 4 6 % respectively The observed standard deviations from the normalised values contain contributions from real time to time variations of the potassium content, from counting statistics of the single measurement and from reproducibility (besides counting statistics) from a single measurement The expected standard deviations from counting statistics alone were 2 7 % and 3 9 % respectively Thus individual time variations departing from the general time variation and reproducibility of the single measurement together account for a standard deviation of about 2 5 % Since the reproducibility of a measurement can be expected to be 1 to 2 % (EVANS 1962) there is not much room for variations of the potassium content This has been established earlier by ANDERSON who found about 2 % standard deviation for the potassium content of a single individual when measured at various times

3 Cesium The spread of ^{137}Cs values has been discussed by, among others, ANDERSON et coll (1962), and ONSTEAD et coll (1960) The latter found standard deviations for the cesium concentration of 24 % (males) and 27 % (females) and for the cesium/potassium ratio of 18 % for males and 31 % for females From the data by ANDERSON et coll one can calculate a standard deviation of 25 % for the cesium/potassium ratio for all adult subjects These results show that for males the cesium/potassium ratio representation gives the smallest spread, which was also found in the present investigation

The most complete report on the variation of the ^{137}Cs content with sex and age has been presented by ONSTEAD *et coll* (1962) *Their results are* represented by the solid curves in Fig 13, and the present experimental results are given with ± 1 SE indicated Since the levels of ^{137}Cs in their investigation differ from ours, the vertical scales for their curves were multiplied by 2 in order to facilitate a comparison of the sex and age trends The sex and age distributions obtained in the present investigation fit, within limits of error, with those given by ONSTEAD et coll (1962)

In the preceding section, the calori consumption was used to reduce the cesium contents of the various groups to comparable quantities This investigation is not detailed enough to provide any information on whether a similar kind of reduction may be obtained by reference to the body content of potassium However, there is some indication that valuable contributions on this issue might be obtained from a study of large groups of growing boys and girls of the same age because of the divergent time variations in their potassium concentrations

Predictions of variations in the body burden with time, based on various data and assumptions, have frequently been published and are partly reviewed in the reports of the United Nations of 1964 and 1966 The discussion in the preceding section has shown that it was possible to get a relatively accurate description of the body burden variation for the groups studied using only milk data for ^{137}Cs, and a similar model should be applicable also to other population groups It cannot be expected that the model employed should be consistent with every single measurement of the body radioactivity of the groups There are variations from place to place of the radioactivity of food, delays between food production and consumption cannot be expected to be covered in all details by the model, dietary habits are different at different times of the year — consumed food in the U S A for instance, in kg per day and capita, varied over the year by about ± 10 % (MICHELSON 1965), ice cream consumption is highest in the summer, Swedes indulge in excessive pork consumption around Christmas (LINDELL & MAGI) and so on — and are also subject to slow changes For instance, it seems as though the peaks predicted

by the model (Fig 11) are less marked in reality Still, this model can be used to give information on the main features of the body burden variation with time and it has been useful for the interpretation of the different time variation patterns found in the different groups It has also given the information that one has to be careful in the interpretation of curves of the body burden variation since activity variations in food (e g pork cereals), which are slow compared to those in milk tend to affect the curve in the same way as slow metabolic rates do HUYCKE & OBERHAUSEN (1964) have assumed that the cesium content of German milk is representative of the aggregate intake by man Using this assumption their calculated curve gave the best fit to the experimentally found one for a biologic half time of 140 d (for persons older than 22 a) It is possible that a more detailed assumption regarding cesium intake would have given a lower value for the biologic half time of cesium In spite of some uncertainties the half times found in this investigation ranging between 55 d and 100 d are in good agreement with those found in Scandinavia and elsewhere as reviewed by LIDEN and by MC CRAW Short half times about 70 d have also been reported recently by GRUNDY & SARGENT (1966) and by STANT et coll (1966)

Refined calculations of the absorbed dose have been made by MIETTINEN et coll (1963) and by MC CRAW For the present purpose it is sufficient to use the value by MIETTINEN et coll of 8 mrad/a per nCi ^{137}Cs/kg body weight Combining this with the potassium concentrations in Table 1 and the cesium/potassium ratios in Fig 4 we find that the highest dose rate to the investigated groups is given to men 1 in September 1964 and is 3 mrad/a This is small compared to the dose rate from radiation from natural sources which amounts to about 100 mrad/a LINDELL & MAGI have given a well balanced discussion of the health aspects of small radiation dose rates like the present ones

Conclusions

On the whole this investigation of cesium and potassium levels in people from Southern Sweden has yielded results in agreement with what has been reported previously Some differing results remain concerning the potassium concentration which may not increase as much for boys and may decrease faster for girls with age than has been reported for corresponding groups of boys and girls in Germany and the USA These problems might deserve further study

It may also be worth pointing out that it has been confirmed that the individual variation from time to time of the potassium content of adults is small the corresponding standard deviation being about 2 % One should also draw attention to the great variability of the potassium content in boys

Much care has been exercised in securing the experimental data This has made possible an analysis of the time variation of the ^{137}Cs burden using milk data collected by others The analysis has yielded results for the biologic half-time which are in general agreement with those expected Analyses of this kind can thus be used as a complement to other methods of studying half times, having the advantage that average half-times for larger groups of people can be obtained For reliable results, much care is necessary both in the experimental procedure and in the analysis

Acknowledgements

Professor Kurt Lidén who suggested this investigation has contributed with many discussions and suggestions throughout the work and it is a pleasure to acknowledge his continuous aid and encouragement Grants from the Swedish Atomic Research Council made the investigation possible

SUMMARY

The potassium and ^{137}Cs content of 57 persons have been followed from February 1964 to September 1966 Each person was measured three times annually The potassium concentration did not increase with age for boys aged 13 to 16 years but decreased faster than expected for girls It was possible to demonstrate age differences in the curves giving ^{137}Cs burden versus time Curves calculated on the basis of milk data for ^{137}Cs described the time variations quite well if the biologic half time for ^{137}Cs was assumed to be 100 ± 30 d for men 80 ± 25 d for women 55 ± 20 d for 14 year old boys and 55 ± 15 d for 14 year old girls

ZUSAMMENFASSUNG

Der Korpergehalt von Kalium und ^{137}Cs ist in der Zeit Februar 1964 bis September 1966 dreimal jahrlich an 57 Personen gemessen worden Die Kaliumkonzentration der Jungen 13 bis 16 Jahre alt nahm mit dem Alter nicht zu die der Madchen aber nahm schneller als erwartet ab Aus Kurven des ^{137}Cs Gehalts in Abhangigkeit von der Zeit konnten Altersdifferenzen gezeigt werden Solche Kurven können mit Hilfe eines Models das nur die ^{137}Cs Konzentration in Milch berüchsichtigt berechnet werden unter der Annahme dass die biologische Halbwertzeit für Manner 100 ± 30 d betragt für Frauen 80 ± 25 d für 14 jahrige Jungen 55 ± 20 d und für 14 jahrige Madchen 55 ± 15 d

RÉSUMÉ

Le contenu du corps humain en potassium et en ^{137}Cs a été mesuré trois fois par an chez 57 sujets de février 1964 à septembre 1966 La concentration en potassium (potassium/poids) a été constante chez les garçons entre 13 et 16 ans mais a diminué plus vite qu on ne s y attendait chez les jeunes filles de 13 à 16 ans On a pu mettre en évidence des différences dues à l âge pour les courbes représentant le contenu en ^{137}Cs en fonction du temps On a

pu aussi calculer des courbes conformes à celles observées en n utilisant que des mesures sur du lait et en supposant une période biologique de 100 ± 30 jours pour les hommes 80 ± 25 jours pour les femmes 55 ± 20 jours pour les garçons de 14 ans et 55 ± 15 jours pour les jeunes filles de 14 ans

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Much care has been exercised in securing the experimental data This has made possible an analysis of the time variation of the ^{137}Cs burden using milk data collected by others The analysis has yielded results for the biologic half-time which are in general agreement with those expected Analyses of this kind can thus be used as a complement to other methods of studying half times, having the advantage that average half times for larger groups of people can be obtained For reliable results, much care is necessary both in the experimental procedure and in the analysis

Acknowledgements

Professor Kurt Lidén who suggested this investigation has contributed with many discussions and suggestions throughout the work and it is a pleasure to acknowledge his continuous aid and encouragement Grants from the Swedish Atomic Research Council made the investigation possible

SUMMARY

The potassium and ^{137}Cs content of 57 persons have been followed from February 1964 to September 1966 Each person was measured three times annually The potassium concentration did not increase with age for boys aged 13 to 16 years but decreased faster than expected for girls It was possible to demonstrate age differences in the curves giving ^{137}Cs burden versus time Curves calculated on the basis of milk data for ^{137}Cs described the time variations quite well if the biologic half time for ^{137}Cs was assumed to be 100 ± 30 d for men 80 ± 25 d for women, 55 ± 20 d for 14 year old boys and 55 ± 15 d for 14 year old girls

ZUSAMMENFASSUNG

Der Körpergehalt von Kalium und ^{137}Cs ist in der Zeit Februar 1964 bis September 1966 dreimal jährlich an 57 Personen gemessen worden Die Kaliumkonzentration der Jungen 13 bis 16 Jahre alt nahm mit dem Alter nicht zu die der Mädchen aber nahm schneller als erwartet ab Aus Kurven des ^{137}Cs Gehalts in Abhängigkeit von der Zeit konnten Altersdifferenzen gezeigt werden Solche Kurven können mit Hilfe eines Models das nur die ^{137}Cs Konzentration in Milch berücksichtigt berechnet werden unter der Annahme dass die biologische Halbwertzeit für Männer 100 ± 30 d beträgt für Frauen 80 ± 25 d für 14 jährige Jungen 55 ± 20 d und für 14 jährige Mädchen 55 ± 15 d

RÉSUMÉ

Le contenu du corps humain en potassium et en ^{137}Cs a été mesuré trois fois par an chez 57 sujets de février 1964 à septembre 1966 La concentration en potassium (potassium/poids) a été constante chez les garçons entre 13 et 16 ans mais a diminué plus vite qu on ne s y attendait chez les jeunes filles de 13 à 16 ans On a pu mettre en évidence des différences dues à l âge pour les courbes représentant le contenu en ^{137}Cs en fonction du temps On a

FROM THE DEPARTMENT OF RADIOTHERAPY B AT THE AKADEMISCH ZIEKENHUIS
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THE ISODOSES OF WEDGE FIELDS

A new reference and calibration system

by

J M Debois

Wedge filters are valuable aids for shaping the isodose distributions according to certain anatomical outlines but there is considerable disagreement on how to present the isodose charts

A reference point in an isodose system serves as a standard point for expressing relative doses at all other points within the field This reference point is situated at the point of maximum dose on the central axis which for telecobalt is 0 5 cm below the surface However the position may be chosen arbitrarily at other points but must be meaningful in a given system or for a given technique of irradiation So it is convenient to take the reference point at the center of rotation in moving beam therapy or at the point of cross fire in the isocentric set up technique When the absolute dose or dose rate is known at this reference point the dose or dose rate at all other points can be calculated For plain fields however it is difficult accurately to measure the dose at the 100% reference point An error in this determination will lead to errors in the whole irradiated volume Oliver & Kemp (1949) and more recently Meredith (1963) have proposed a calibration point for

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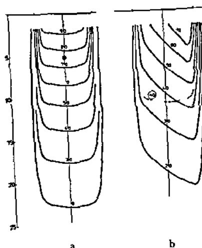


Fig 1 Telecobalt SSD 80 cm 7 cm × 7 cm fields Standard isodoses at 5 cm reference point 7b 2 (left) and isodoses for a wedge field according to our reference system the step wedge calibration referring to the standard isodos

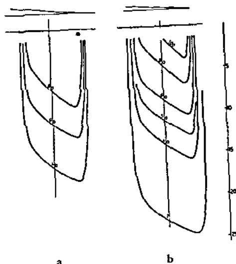


Fig 2 Isodoses for a wedge field with the 100 calibration point at the center of the field (right) and at the toe of the wedge field (left)

one isodose line i e the 50% one is plotted again at another place on the paper where the wedge isodose will be traced (Fig 1) Without changing the calibration setting of the plotter and the position of collimator and phantom, the wedge is placed beneath the collimator The wedge is in the correct position when the light of the field at the toe is just about to disappear (9) Then the isodoses of the wedge field are plotted Because of the absorption due to the filter all the isodoses will be shifted in the direction of the surface with a typical slope

The previous tracing of the plain 50% isodose curve enables us to place the axis of the field simply by superposition of the wedge distribution on the plain field distribution By the same way one can determine the absorption factor by the wedge at the axis This absorption is constant along the axis and so the dose rate and the treatment time can easily be computed from the appropriate value of the plain field The ICRU recommendations (2) however (Chapter III section D 13 and 17) are not in complete agreement with this system In our system the 100% reference point is at the axis of the plain field which we consider now as modified by the introduction of the filter

plain fields at 5 cm depth, and this has been taken over in the ICRU recommendations (2) The link between these two points, the reference point and the calibration point, is provided by the depth dose table When a wedge field is used, the same problems with respect to reference and calibration are present

Usually, the 100% reference point of a wedge field is on the axis of the field, at a build up level near the surface (1) This agrees with the recommendations of the ICRU Other reference points are given in the literature, however For example, JOHNS (1962), POURQUIER (1957), and WELKER (1965) have set the 100% value at the 'toe of the wedge field, at the edge near the surface KUTTIG (1965) gives no precise indication in his paper, but from his figures it may be assumed that the 100% reference value was at a certain distance from the edge of the field If the first convention is the most widely accepted, the existence of the other methods demonstrates the problem connected with the reference point

The best point of reference for a wedge field is situated at the axis, according to the ICRU recommendations There is no reason for locating the calibration point elsewhere than at a depth of 5 cm For the calibration we then need the depth dose curve at the axis Consequently, an axis depth dose table should be established, or be available, for every wedge This is relatively easy when only a few wedges are in use in a radiotherapy department, but for departments without adequate facilities it will be almost impossible The dosimetric work is almost endless when many wedges and different radiotherapy apparatus are in use This is especially the case with a variable step wedge which offers many possibilities For every combination of wedge steps and for every field size we need an axis depth dose curve for the calibration

We have been looking for a method that would eliminate the determination of all these values and also without the experimental errors involved in this sequence

A reference and calibration system

The system is based on the following facts (1) accurate and reliable depth dose tables exist only for plain fields and not for wedge fields unless they are measured for each individually, (2) a wedge filter modifies the dose distribution of a plain field of the same size

So the dose distribution of a wedge field could be coupled with the corresponding plain field This method is very easy with our automatic isodose plotter (3) but can in fact be adapted for all other methods of isodose plotting First, a 'plain' field calibration is carried out with the center of the ionization chamber at 5 cm below the surface The isodoses are plotted completely, and

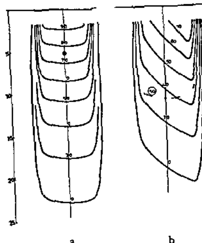


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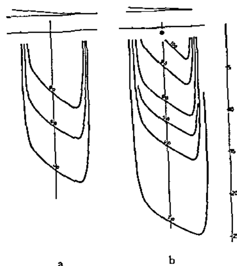


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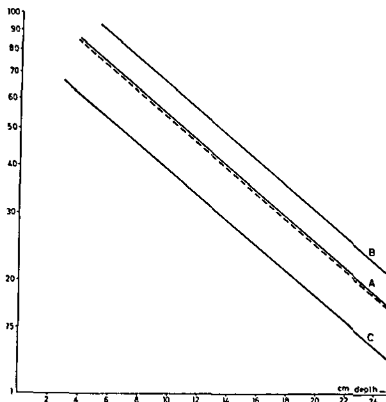


Fig 3 Telecobalt SSD 80 cm field 7 cm × 7 cm Comparison of the depth dose curves of the different systems Wedge field (—) open field ( ) 100 at 0 5 cm center (A) 100% at the toe (B) and according to our system (C)

The advantages of this system are as follows

1 The method simplifies the dosimetric work of measuring central axis depth doses, drawing isodoses and calibrating the output for each wedge filter and field

2 The system allows a more rapid exploration of all the different possibilities of a variable step wedge From the different isodoses obtained a more appropriate selection of the distribution of interest can be made

3 When the manufacturer of a wedge filter delivers these isodoses the radiotherapist need not determine the absorption factor for the calculation of treatment time The filter must of course be used at a specified distance and on the same machine

4 Another advantage is that the radiotherapy technician can use only the one time dose list of the plain fields So the isodose correctly applies to the given (or applied) dose and the time dose errors are minimized

Conversion of the isodose curves to conform to the ICRU recommendations We mentioned earlier that the isodoses of a wedge field in our system were displaced toward the surface with a constant factor This factor is also called the transmission factor of the filter and depends of course on the wedge and the opening of the diaphragm

When we plotted the central axis depth doses of a wedge field according to our system we found that they form a straight line wich runs parallel with the line of the plain field It runs parallel because the transmission factor is constant along the whole depth This is shown on the graph of Fig 3 where the axis depth doses of the isodoses of Figs 1 and 2 have been plotted The depth dose curve at the axis is identical for a plain field and a wedge field with the same diaphragm setting when the 100% is set on the axis as recommended by the ICRU This is not surprising Wedge filters are indeed also used for correcting oblique incidence where the axis depth dose is also unchanged

This leads to a very important consequence It means that a wedge field distribution can be calculated when the exact physical dimensions of the filter are known On the other hand the isodose distribution for a wedge filter can be drawn by an automatic isodose plotter, by calibrating it at 5 cm depth with the same value as given in tables for plain fields We can thus rely simply on these tables without first performing axis depth dose measurements

All wedge field isodose graphs can thus be standardized according to the ICRU recommendations and based on normal depth dose values

Addendum in proofs

After the article was submitted a similar work has been published by ARON & SCAPICCHIO (Amer J Roentgenol 96 (1966), 70) who reached essentially the same conclusion concerning the axis depth dose

Acknowledgement

We wish to thank S W J Meridith J Dutreix and especially M Cohen for helpful suggestions

SUMMARY

The different reference systems used for wedge fields are compared and a simple reference system is proposed Although this system does not conform to the ICRU recommendations it has some advantages mainly for a rapid survey of the possibilities of a variable step wedge filter The fact that the axis depth doses of all systems run parallel leads to the important conclusion that the axis depth dose of a plain field can be applied to wedge fields Therefore a uniform system in agreement with the ICRU recommendations can be established

ZUSAMMENFASSUNG

Die verschiedenen fur Keilfilter angewendeten Referenzsysteme werden verglichen und ein einfaches System wird vorgeschlagen Trotzdem dass dieses System nicht mit den Empfehlungen der ICRU übereinstimmt hat es gewisse Vorteile da ein schneller Überblick uber die Moglichkeiten die sich bei der Anwendung von variablen Keilfilteren erbieten erhalten werden kann Da bei allen Systemen die Tiefendosis Kurven an der Achse parallel laufen kommt man zu dem Schlussatz dass die gewohnlichen Dosistabellen auch bei der Anwendung von Keilfiltern benutzt werden konnen Auf diese Weise kann ein uniformes System in Übereinstimmung mit den ICRU Rekommandationen erreicht werden

RÉSUMÉ

Les différents systèmes de référence utilisés pour les filtres en coins sont comparés et un nouveau système plus simple est proposé Malgré qu il ne soit pas tout à fait conforme aux recommendations de l ICRU il compte un certain nombre d avantages surtout pour une rapide analyse des possibilités d un filtre variable Le fait que les doses à l axe de tous les systèmes utilisés sont des lignes parallèles permettent de tirer une conclusion très importante les tables des doses à l axe pour un champ normal peuvent être utilisées pour les filtres en coins Ainsi un système uniforme et conforme aux recommendations de l ICRU peut être établi

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FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR ASSOC PROF G HETTINGER), UNIVERSITY OF UMEA SWEDEN

MEASUREMENT OF DOSES FROM HIGH ENERGY ELECTRON BEAMS AT SMALL PHANTOM DEPTHS

by

H SVENSSON and G HETTINGER

Experimentally determined depth dose curves show great discrepancies at small phantom depths (LAUGHLIN et coll 1953 HSIEH & UHLMANN 1956 v d DECKEN 1956 WURTHNER & FROST 1964) HSIEH & UHLMANN found the surface dose to be 60 % to 85 % of the dose at dose maximum with electron energies between 10 and 35 MeV and WURTHNER & FROST determined the surface dose in the same energy range to be between 90 % and 93 %

The discrepancies may depend on differences in the spectral distribution of the electrons When electrons pass the scatterer and transmission chamber and when they are scattered against the walls of the treatment applicator low energy electrons are produced (MARKUS 1960 LOEVINGER et coll 1961, SVENSSON & HETTINGER to be published) The surface doses may also differ because of variations in the constructional details of different accelerators However the differences between reported values of measurement may partly be due to technical difficulties Plane parallel ionization chambers or photographic film are usually employed for dose measurements at small phantom depths The measurement of ionization may be difficult in the build up region (JOHNS

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ZUSAMMENFASSUNG

Die verschiedenen für Keilfilter angewendeten Referenzsysteme werden verglichen und ein einfaches System wird vorgeschlagen Trotzdem dass dieses System nicht mit den Empfehlungen der ICRU übereinstimmt hat es gewisse Vorteile da ein schneller Überblick uber die Möglichkeiten die sich bei der Anwendung von variablen Keilfilteren erbieten erhalten werden kann Da bei allen Systemen die Tiefendosis Kurven an der Achse parallel laufen kommt man zu dem Schlussatz dass die gewöhnlichen Dosistabellen auch bei der Anwendung von Keilfiltern benutzt werden können Auf diese Weise kann ein uniformes System in Übereinstimmung mit den ICRU Rekommandationen erreicht werden

RÉSUMÉ

Les différents systèmes de référence utilisés pour les filtres en coins sont comparés et un nouveau système plus simple est proposé Malgré qu il ne soit pas tout à fait conforme aux recommendations de l ICRU il compte un certain nombre d avantages surtout pour une rapide analyse des possibilités d un filtre variable Le fait que les doses à l axe de tous les systèmes utilisés sont des lignes parallèles permettent de tirer une conclusion très importante les tables des doses à l axe pour un champ normal peuvent être utilisées pour les filtres en coins Ainsi un système uniforme et conforme aux recommendations de l ICRU peut être établi

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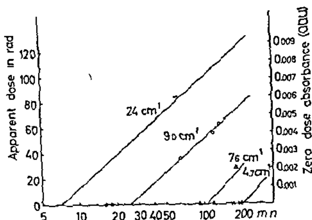


Fig 2 Absorbance of non irradiated ferrous sulphate solution due to storage effects as a function of time The surface to-volume ratio is used as parameter The irradiation cells used in the present dose measurements at small depths had a surface to-volume ratio of 24 cm⁻¹

The optical density at 304 nm was measured with a Beckman Du spectro photometer supplied with micro equipment Volumes (amounts of liquid) down to about 0 3 ml can be measured The irradiation cells should contain about 0 4 ml however to enable rinsing of the irradiation cells as well as of the sucking device with the same dosimeter solution as the one to be measured

When dosimeter solution is stored in polystyrene cells, a reaction takes place which can be read off photometrically as increased absorbance (KARZMARK et coll 1960) This absorbance which we call zero dose absorbance increases with storage time and surface to volume ratio as may be seen from Fig 2 The irradiation cells used in the present investigation have a large contact surface between dosimeter solution and cell wall the surface to-volume ratio being about 24 cm^{-1} After storing the dosimeter solution for 2 hours in these cells the zero dose is about 100 rad

After storage the chemical response has also been increased after two hours it has augmented about 3 % for a surface to-volume ratio of about 24 cm^{-1} The measurement values will therefore have to be corrected both for zero dose absorbance and for increase in response A study of the dependence on storage of the zero dose absorbance and response has been reported in detail elsewhere (SVENSSON PETTERSSON & HETTINGER 1967)

The best reproducibility is obtained when storage time is short since then the zero-dose absorbance and increase in response are small A reproducibility

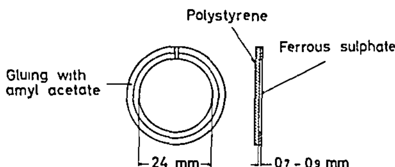


Fig. 1. Irradiation cells of polystyrene for measurement of the dose at small phantom depths.

et coll. 1958). As the spectral distribution of electrons change with depth in the phantom, it is necessary to employ different calibration factors at the various depths for conversion of the measured ionization into dose. The change with depth of the spectral distribution is particularly great for the first millimetre from the surface.

The energy dependence of the ferrous sulphate dosimeter is slow, which renders it suitable for dose measurements at small phantom depths. In the present paper, the use of dosimeters with a layer of liquid of between 0.7 mm and 0.9 mm in the measurement of dose distribution at small phantom depths will be described, and the influence on the response of the irradiation cells and the measurement time will be discussed.

Technique. A polystyrene phantom, size 25 cm × 25 cm × 30 cm, was used. As the linear cross section for electron interactions in polystyrene and water is almost the same, the depth dose curves determined in a polystyrene phantom may be supposed to be valid also for water. The irradiation cells were made of unmodified polystyrene, the dimensions of which are shown in Fig. 1. The cell wall facing the radiation beam is 0.1 mm thick, and the cells are glued together with polystyrene dissolved in amyl acetate. Newly made cells are stored for at least two days in vacuum so that all remains of the volatile amyl acetate disappear; they are then filled with dosimeter solution and stored for at least a week. Before they are taken into use, they are further rinsed repeatedly with dosimeter solution; during storage the cells are always filled with dosimeter solution (PETTERSSON & HETTINGER 1967). A sucking device is used when transferring the dosimeter solution to and from respectively the photometer and the irradiation cells. By means of this device, the irradiation cells can be rinsed rapidly 2 to 3 times before each irradiation; this was found to be necessary in order to maintain good reproducibility.

SUMMARY

Ferrous sulphate dosimeters were used for the measurement of doses at small phantom depths the layer of the liquid being between 0 7 mm and 0 9 mm The influence of irradiation cells and measurement time on the response are discussed

ZUSAMMENFASSUNG

Es wurden Eisensulfatdosimeter fur die Messung der Dosisverteilung im Phantom bei geringen Tiefen benutzt die Dicke der Messflussigkeit betrug 0 7 mm bis 0 9 mm Der Einfluss der Strahlungszellen und des Zeitfaktors wird besprochen

RESUMÉ

Les auteurs ont utilisé des dosimètres à sulfate ferreux pour mesurer les doses a de petites profondeurs dans les fantomes la couche de liquide mesurant de 0 7 mm a 0 9 mm Ils examinent l influence des cellules d irradiation et du temps de mesure sur les résultats

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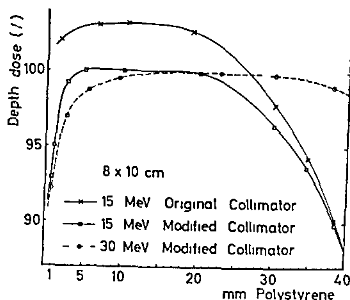


Fig 3 Relative depth dose measured along the central axis in a polystyrene phantom exposed to 15 or 30 MeV electrons

better than ± 1 5 % can be obtained at 3 000 rad with a surface to volume ratio of 24 cm^{-1}, if filling, irradiation and evaluation of the dosimeter can be achieved in less than half an hour

Conclusion

By means of the measurement technique described it has been possible to study the influence at small depths of the treatment tube on the dose distribution from electron radiation With the original tube of the betatron (BBC Asklepitron 35) the dose was found to be between 1 % to 2 % lower at 0 5 mm depth than at dose maximum, using a field size of 8 cm × 10 cm and electron energies between 15 and 30 MeV (Fig 3) With the modified collimator, i e by replacement of the treatment tube with a brass disk placed close to the patient (Svensson & Hettinger, to be published), the dose was found to be 8 % to 10 % lower than at dose maximum with field sizes larger than 6 cm diameter If the brass disk is placed at SSD 130 cm, i e at 20 cm greater distance than is usual, the skin dose is diminished by a further 5 % to 10 % The skin reactions observed with this greater SSD are less than when the collimation is carried out with a perspex tube

SUMMARY

Ferrous sulphate dosimeters were used for the measurement of doses at small phantom depths the layer of the liquid being between 0 7 mm and 0 9 mm The influence of irradiation cells and measurement time on the response are discussed

ZUSAMMENFASSUNG

Es wurden Eisensulfatdosimeter fur die Messung der Dosisverteilung im Phantom bei geringen Tiefen benutzt die Dicke der Messflussigkeit betrug 0 7 mm bis 0 9 mm Der Einfluss der Strahlungszellen und des Zeitfaktors wird besprochen

RÉSUMÉ

Les auteurs ont utilisé des dosimètres a sulfate ferreux pour mesurer les doses a de petites profondeurs dans les fantomes la couche de liquide mesurant de 0 7 mm à 0 9 mm Ils examinent l influence des cellules d irradiation et du temps de mesure sur les résultats

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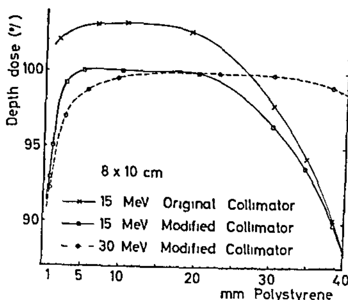


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EFFECT OF COMPLAMIN ON RADIATION-INDUCED ERYTHEMA

by

G NOTTER, T TSIOULIAS and P-E ÅSARD

A difference in the degree of dermal erythema has been demonstrated between the areas above and below the second intercostal space The difference is significant for both spontaneous erythema (blushing) and for mechanically (rubbing) or chemically (mustard oil) induced erythema (ADAMS RAY 1952), it is probably due to a congenitally higher sympathetic tonus, causing vaso constriction and reduced blood flow in the skin of the area below the second intercostal space

The same difference in dermal erythema could also be demonstrated photometrically during and after irradiation of the supra and infra clavicular region (NOTTER et coll 1965) With the photometric method then used it was possible to measure the grade of dermal erythema The method can thus be applied for instance to investigate the possible radiation protective effect of certain drugs on skin reactions following radiologic treatments In the present study, the influence of Complamin® (Tika) (7-/2 hydroxy 3 (N 2 hydroxy ethyl N methyl amino]propyl/theophyllin nicotin), was examined This

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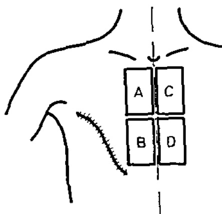


Fig 1 Two parasternal irradiation fields A and B and reference fields C and D The measuring points were in the middle of the fields

substance was stated by BARTH & KERN (1963) to have some protecting effect when mice were subjected to irradiation but this has not been confirmed in later investigations performed by NELSON & RONNBACK (1965) It therefore seemed of interest further to investigate the protective effect of Complamin for example on dermal erythema in the therapeutic irradiation of human subjects

Material and Methods Twenty one patients with breast cancer were post operatively irradiated in the parasternal region with 12 MeV electrons from a Siemens 17 MeV betatron they received 10 × 400 rad in 22 days to two fields 6 cm × 8 cm (Fig 1) The patients were divided into two groups 10 patients as controls and 11 patients who orally received 3 × 0 9 g Complamin daily from three days before radiation treatment and during the whole investigation period

The measurement of differences in the grade of erythema was performed with the same apparatus and technique as in the previous investigation (NOTTER et coll 1965) In such measurements the principle is that a skin area 2 cm in diameter is illuminated with light in the 550 mμ range in which range hemoglobin has a strong absorption band A measure of the redness of the skin is obtained as the recorded intensity of the light reflected from the skin The intensity is measured by means of a photocell built into a measurement probe which also contains the lamp and an interference filter Details of the apparatus were given in the report on the previous investigation

Measurements were performed before and immediately after the first treatment on fields A and D in Fig 1 and then 14 days after completion of

Table

Differences in skin redness between fields C and A and D and B

	Number of patients	C/i_A	D/i_B
Before irradiation			
Control group	10	0.99 ± 0.014	0.98 ± 0.016
Complamin group before Complamin intake	11	1.03 ± 0.013	1.02 ± 0.014
Complamin group after three days intake	11	1.01 ± 0.015	1.02 ± 0.016
Immediately after last irradiation			
Control group	10	1.11 ± 0.024	1.06 ± 0.028
Complamin group	10	1.19 ± 0.023	1.15 ± 0.029
Fourteen days after last irradiation			
Control group	9	1.13 ± 0.030	1.10 ± 0.031
Complamin group	9	1.17 ± 0.032	1.15 ± 0.035

the treatment. To clarify if Complamin alone caused the difference in skin redness between fields C A and D B the Complamin treated group was measured twice before the first treatment, namely before and after they had started to receive Complamin. Fields C and D in Fig. 1 were used as reference fields, as they had not been irradiated. Field C was compared with field A, and field D was compared with field B, by taking the ratio between the photogenerated currents C/i_A and D/i_B, respectively, as a measure of the difference in redness between the two fields. If, for instance, $C/i_A > 1$, it means that field A has a stronger redness compared with field C. If Complamin can lower the degree of radiation induced erythema then the differences in redness between fields C A and D B ought to be less marked for the Complamin group in comparison with the control group.

Results

The results of the measurements are recorded in a Table and in Fig. 2. The spread indicated in this table and in the figure represents the standard deviation of the mean. The differences before treatment between fields C A and D B are approximately zero, as expected. This holds also for the Complamin group after an oral dose of 2.7 g Complamin per diem for three days. Immediately after, and 14 days after, the last treatment, the measurements showed a difference between the reference fields and the irradiated

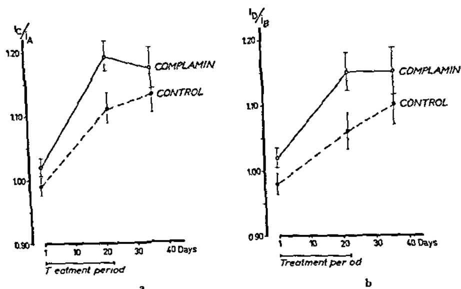


Fig 2 Difference in skin redness (a) between fields C and A and (b) between fields D and C The standard deviations of the means are indicated

fields which for fields A and B was due to the radiation induced erythema This relative difference was higher in the Complamin group as compared with the control group which indicates the existence of a more intense erythema for the Complamin treated patients The difference between the two groups was highest in the measurements performed immediately after the last treatment

When applying the t test no statistically significant difference between the two groups was obtained in the measurements before irradiation or 14 days after the last treatment but in the measurements made immediately after the last treatment the difference was almost significant ($2\% < p < 5\%$) for both I_C/I_A and I_D/I_B

Discussion

Complamin may in theory either increase or decrease the development of radiation erythema (1) it may cause a decrease by its general radiation protective effect as claimed by BARTH & KERN (1963) or (2) it may cause an increase because of the vasodilatory effect of its theophylline and nicotinic acid components on the arteries and capillaries of the skin

No signs of any radiation protective effect of Complamin i e a decrease in

the radiation erythema, could be observed under the experimental conditions prevailing in the present study The difference between the mean values for the control group and the Complamin group are almost statistically significant for the measurements made immediately after the last treatment This seems to indicate that Complamin may even increase the radiation erythema because of hyperemia and probably because of increased pO tension

SUMMARY

The effect of Complamin given in an oral dose of 2 7 g per diem on the development of radiation erythema was examined in 11 patients and compared with 10 controls No radiation protective effect of Complamin on the skin was apparent

ZUSAMMENFASSUNG

Die Wirkung oraler Verabreichung von Complamin in einer taglichen Dosis von 2 7 g wurde mit Hinsicht auf die Entwicklung von Bestrahlungs Erythem an 11 Patienten und 10 Kontrollen gepruft Es konnte keine Schutzwirkung auf die Haut festgestellt werden

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Les auteurs ont examiné sur 11 malades comparés a 10 témoins l effet de la Complamine donnée par voie buccale à la dose de 2 7 g par jour sur l évolution de l érythème du aux radiations Ils n ont noté aucun effet radio protecteur de la Complamine sur la peau

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FRACTIONATION IN RADIOTHERAPY OF CANCER OF THE LIP

by

J S MITCHELL and L MARY MITCHELL

In recent years there has been a revival of interest in the problem of fractionation in radiotherapy particularly from the radiobiologic point of view The need for evidence from much more clinical material for exact analysis has become apparent (STRANDQUIST 1963 and Preliminary and Progress reports of the Working Party of the British Institute of Radiology 1963 1964) It is important to mention the work of KOLLER and SMITHERS (1946) on the use of cytologic examinations in attempts to determine the minimum dose and optimal fractionation for individual tumours It is of particular interest to refer to the studies by BARTH and KERN (1961) on the optimal irradiation interval in roentgen therapy of carcinoma of the lip there was suggestive evidence that 48 hour intervals were advantageous

The present contribution is limited in scope and deals with the influence of fractionation on the results of a particular technique of roentgen therapy The evidence is based on a retrospective study of the treatment in 215 selected cases of primary carcinoma of the lower lip in men in the years 1946—1959

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Table 1

Physical factors and dosage — Roentgen therapy at 220 kV, 15 mA HVL 1 5 mm Cu filter 1 mm Cu + 1 mm Al, FSD 40 cm single field — Total minimum tumour dose at depth d cm = 3 750 R delivered in seven equal fractions each 536 R in an overall time of 8 days

Field diameter cm	Total skin dose (R) for depth d		
	0 5 cm	1 0 cm	1 5 cm
2 5	3 990	4 310	4 680
3 0	3 970	4 220	4 550
3 5	3 940	4 120	4 470
4 0	3 910	4 070	4 310
4 5	3 870	4 030	4 260
5 0	3 830	3 950	4 170

inclusive In these cases, there was histologic proof of squamous carcinoma, and there was no evidence of lymph node metastases at the time of treatment There appear to be large and statistically significant differences between the results using certain different schemes of fractionation with the same total minimum tumour dose' and the same 'overall time of treatment Moreover, there was an apparently unbiased allocation of patients to the different schemes of fractionation

Technique The technique may be summarised as the radical radiotherapy of localized primary carcinoma of the lip by means of filtered 200—220 kV roentgen rays of HVL 1 4 to 1 5 mm copper with a minimum tumour dose of 3 750 R delivered in 7 equal fractions, each 536 R, in an overall time of 8 days The dose rate was in the region of 30 to 45 R per minute with FSD always 40 cm, usually the lesion was treated by means of a 5 cm × 5 cm applicator, with individual lead cut outs and lead wrapped in sterile gauze placed in the mouth behind the lip to protect the deeper tissues

This technique was introduced in 1938 and has not changed since 1943 It was developed to be analogous to the Manchester two plane moulded radium applicator (PATERSON and PARKER 1934 MEREDITH 1949), and in a slightly different form was first described in a clinical investigation of skin reactions (MITCHELL 1940) Until November 1955, the total minimum tumour dose was prescribed as 3 500 R It was then established, as a result of measure ments by the National Physical Laboratory (see PATERSON 1956), that the correct value of this dose was almost exactly 3 750 R For the roentgen radia tion used, assuming a value of 0 96 rad per R in water (ICRU NBS (1956)

Table 2

Schemes of fractionation — Total minimum tumour dose in all cases = 3 750 R delivered in seven equal fractions in an overall time of 8 days

Designation	Days of treatment and minimum tumour dose delivered						
	M	Tu	W	Th	F	Sa	Su
5 002	— 536 R	— 1 071 R	— 1 607 R	— 2 143 R	— 2 679 R		
	— 3 214 R	— 3 750 R					
2 005				— 536 R	— 1 071 R		
	— 1 607 R	— 2 143 R	— 2 679 R	— 3 214 R	— 3 750 R		
3 004			—	—	— 1 607 R		
	—	—	—	— 3 750 R			
4 003		—	—	—	— 2 143 R		
	—	—	— 3 750 R				

Handbook 62 Table 2 p 17) the corresponding value of the absorbed dose is 3 600 rad According to RAKOW (1965) the relevant value for muscle is 0 946 rad per R so that the corresponding absorbed dose is 3 550 rad

However from a practical point of view it is simplest to continue to specify the total minimum tumour do e at a depth of d cm below the anterior skin surface as 3 750 R and calculate the total skin dose for the field diameter used as exemplified in Table 1 The fields of course were often not circular In general a margin of 0 5 cm of apparently normal tissue was allowed around the visible lesion at the surface and also as far as could be estimated below the lesion in order to calculate the minimum tumour dose It is inevitable that errors and inconsistencies could be introduced in this calculation by the difficulty of estimating the thickness of the lesion

Fractionation The original technique was planned so that treatment started on a Monday 5 daily treatments were given from Monday to Friday inclusive then there was an interval without treatment on Saturday and Sunday and

two further treatments were given on the following Monday and Tuesday Histologic studies of serial biopsy specimens of the tumours by A Glucksmann of the Strangeways Research Laboratory, Cambridge (see ref GLUCKSMANN 1941) showed that in general, after the first 5 treatments, the proportion of cells in mitosis was reduced to a very low level The development of this method of treatment was also influenced by the serial histologic studies of CHEVAL and DUSTIN (1931) and by the technique of 'einfach fraktionierte Kurzbestrahlung described by SCHINZ and ZUPPINGER (1937)

However, pressure of work and administrative difficulties led to the practice of starting the treatment on any day that was possible The immediate results appeared to be very satisfactory and the stages involved in the development of the method were forgotten With the resumption of radiotherapy in Cambridge in 1946, the treatments by this method were started when convenient, usually on Mondays or less frequently on Thursdays, but sometimes on Tuesdays or Wednesdays As far as can be ascertained, there was no bias apart from administrative convenience in the choice of the starting day and no difference in the technique for different starting days

It seems reasonable to assume that the practice of starting treatments on different days resulted in a form of random allocation of patients to one of the four schemes of fractionation, which are described in Table 2 The schemes differ in the total dose delivered before the interval of about 72 hours in the course of treatment In this respect the greatest difference is between the schemes 5 002 and 2 005

In about 1960 it appeared that patients treated with fractionation scheme 5 002 were remarkably free from recurrences and particularly from fatal recurrences This impression was the starting point for the present investigation, and, with the exception of the patients over the age of 70 with the larger lesions, has been confirmed

It may be mentioned here that a great deal of effort has been devoted to examining factors, which might have introduced bias in the allocation of patients No evidence has been found for this In fact, any loading tended to suggest perhaps slightly less favourable conditions for the treatments 5 002 For example, the net proportion of these patients, aged 70 years and over, was 30/85, i e 35 3 %, while the corresponding proportion for all the other patients was 27/98, i e 27 6 %, this difference is not statistically significant ($\chi^2_c = 0\ 937$, for 1 d f $P = 0\ 333$)

Further, it may be mentioned that of the 9 patients aged 80 years and over, seven were treated with scheme 5 002, and five of these developed recurrences which proved fatal, the other two patients were treated with scheme 4 003, and one of these had a recurrence which was fatal

Table 3

Numbers of patients treated and numbers of recurrences at 5-year follow-up — Histologically verified cases of primary squamous carcinoma of lower lip in men treated by 8 day roentgen therapy in the years 1946—1959

Scheme of fractionation	Initial number	Net number	Number of recurrences (all sites)	Number of fatal recurrences
5 002	10?*	85	12	8
4 003	27	24	7	3
3 004	33	26	7	2
2 005	53	48	19	7
All schemes	215	183	45	20

* Including one patient untraced

The net number was obtained by excluding from the initial number treated those dying without recurrence at any site within 5 years

In addition of 12 cases with no biopsy and 7 cases with inconclusive biopsy none died within 5 years of any cause one further unproved case was untraced after 3 years

Selection of patients In general during the years 1946—1959 inclusive the method of 8 day roentgen therapy described was the routine method of treatment of primary carcinoma of the lip in patients referred under the age of 70 with no metastatic nodes at the time of treatment Only four patients were treated by means of radium moulds and none since 1951 In patients over the age of 70 small lesions were often treated with roentgen therapy with single large doses and large lesions either at palliative levels with single doses or spaced single doses or at radical levels by means of fractionated doses with an overall time between 3 and 6 weeks

The present investigation is limited to the study of the results of the routine method of 8 day roentgen therapy in histologically verified cases of primary squamous carcinoma of the lower lip in men with no clinical evidence of metastatic nodes at the first treatment

The selection of the patients for inclusion in this investigation may be clarified further by listing the categories excluded as follows

1 Cases treated by any form of surgery other than biopsy

2 Cases in which the overall time of the roentgen therapy was not 8 days or in which less than seven fractions were delivered in an overall time of 8 days

3 Cases treated by gamma rays of radium iridium 192 or caesium 137

4 Cases in which there was previous treatment by surgery or irradiation for any malignant lesion of the lips

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other case responded to treatment 2 005 but $11\frac{1}{2}$ years later has developed what appears to be an edge recurrence, which has been excised Of the ten cases with lesions reported as moderately well differentiated eight received treatment 5 002 of these, six survived without recurrence more than 10 years though one of these has developed an edge recurrence after 17 years and 5 months one died with lymph node metastases after 3 years and one died after 11 months with residual carcinoma at the primary site despite further treatment by means of a radium mould The other two cases both received treatment 3 004 and survived 12 years without recurrence Accordingly, of the net number of 85 cases receiving treatment 5 002, eleven had poorly differentiated or moderately differentiated lesions while the comparable numbers were two out of 26 cases treated with scheme 3 004 and one out of 48 cases treated with scheme 2 005 It is difficult to believe that differences in histological grading could introduce bias in favour of treatment 5 002

Assessment of results

For comparison of the results of treatment with the four different schemes of fractionation the simplest method appears to be comparison of the recurrence rates (Table 3) It is important to estimate not only the frequency of recurrences at all sites (see Table 5) but also the frequency of fatal recurrences Recurrences when they occur are of course treated by the most suitable methods but nevertheless in 20 patients out of the 45 who developed recurrences the recurrence proved fatal

For the present purpose the best way to deal with the problem of deaths from intercurrent disease appears to be to estimate the net recurrence rate at the 5 year follow up It is considered that the crude recurrence rate based on the initial number of patients treated could be misleading The net number is obtained by subtracting from the initial number treated those dying without any form of recurrence of carcinoma of the lip within 5 years after treatment

In estimating the number of recurrences at the 5 year follow up it is to be noted that two cases both originally treated with scheme 3 004 have been included and in these cases it was assumed that the recurrences were present at 5 years after the initial treatment although the recurrences first received roentgen therapy at 5 years and 6 months and at 5 years and 9 months The sites of these recurrences were at the edge of the treated field and at the regional lymph nodes respectively It is important to mention that in the whole series no further recurrences have been observed until 9 years and months or later after treatment The six late recurrences observed between

5 Lesions of other histologically determined type than squamous cell carcinoma, in particular, lesions of the following types have been excluded keratoacanthoma (molluscum sebaceum), squamous cell papilloma, basal cell carcinoma, basosquamous carcinoma The nomenclature follows the usage of UICC Illustrated Tumor Nomenclature (1965)

6 Lesions with no biopsy or unsatisfactory biopsy It is of interest (see Table 3) that these cases responded extraordinarily well

7 Lesions of the upper lip Involvement of the angle of the mouth by a carcinoma arising on the lower lip is not excluded

The *size* of the lesion has been classified on the basis of the maximum dimension (see Table 4) It is of interest that evidence has been presented recently to show that 'nothing is gained by using measurements other than the maximum diameter" of tumours (GURLAND and JOHNSON 1966) The proportion of lesions with maximum diameter 3 0 cm and greater (group D) increases with age There were none among the 27 patients under 50, 6 among the 99 in the age group 50—69 and 10 among 57 patients aged 80 and over Among the group D patients, there were three with lesion of maximum dimension greater that 4 0 cm, viz one aged 85 with maximum dimension of lesion 6 0 cm who survived 9 years without recurrence after treatment 5 002, one aged 74 with maximum dimension of lesion 5 0 cm who survived without recurrence 8 years after treatment 3 004 and one aged 69 with maximum dimension of lesion 4 5 cm who died after an edge recurrence at 2 years and 8 months after treatment 2 005

The *staging* of the cases follows the application of the TNM system to carcinoma of the lip, as dicussed by COCCHI and HAAB (1960) Groups A and B corresponding to T_1Na and T_2Na taken together, are classified as stage I, groups C and D, corresponding to T_3Na, are classified in stage III

Histological grading of squamous carcinoma of the lip is difficult, because as a rule only small biopsy specimens are available EBENIUS (1943) concluded that 'the degree of cornification as diagnosed from small biopsy specimens can scarcely be made the basis of the determination of the degree of malignancy of the tumour or the prognosis" In the present net group of 183 histologically verified cases of squamous carcinoma of the lower lip in men (see Table 3), 4 were reported as poorly differentiated and 10 as moderately well differentiated, the other 169 cases were regarded as well differentiated squamous carcinoma Of the 4 cases with poorly differentiated lesions, 3 received treatment 5 002, with two ten year survivals without recurrence and one death within one year after unsuccessful block dissection of regional gland metastases, the

other case responded to treatment 2 005 but 11½ years later has developed what appears to be an edge recurrence, which has been excised Of the ten cases with lesions reported as moderately well differentiated, eight received treatment 5 002 of these six survived without recurrence more than 10 years though one of these has developed an edge recurrence after 17 years and 5 months, one died with lymph node metastases after 3 years and one died after 11 months with residual carcinoma at the primary site despite further treatment by means of a radium mould The other two cases both received treatment 3 004 and survived 12 years without recurrence Accordingly of the net number of 85 cases receiving treatment 5 002 eleven had poorly differentiated or moderately differentiated lesions while the comparable numbers were two out of 26 cases treated with scheme 3 004 and one out of 48 cases treated with scheme 2 005 It is difficult to believe that differences in histological grading could introduce bias in favour of treatment 5 002

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In estimating the number of recurrences at the 5 year follow up it is to be noted that two cases both originally treated with scheme 3 004 have been included and in these cases it was assumed that the recurrences were present at 5 years after the initial treatment although the recurrences first received roentgen therapy at 5 years and 6 months and at 5 years and 9 months The sites of these recurrences were at the edge of the treated field and at the regional lymph nodes respectively It is important to mention that in the whole series no further recurrences have been observed until 9 years and 6 months or later after treatment The six late recurrences observed between 9

Table 4

Influence of age and size of lesion on the frequency of recurrences at 5-year follow up — Histologically verified cases of primary squamous carcinoma of the lower lip in men treated by 8 day roentgen therapy with the four schemes of fractionation in the years 1946—1959

Age at treatment (years)	Groups	Schemes of fractionation: 5 002			4 003		
		Net number	Number of recurrences	Number of fatal recurrences	Net number	Number of recurrences	Number of fatal recurrences
Less than 50	A	1	0	0	0	0	0
	B	11	1	0	4	1	1
	C	1	0	0	1	0	0
	D	0	0	0	0	0	0
	All	13	1	0	5	1	1
50—69	A	13	0	0	4	0	0
	B	24	1	0	5	2	1
	C	4	0	0	1	0	0
	D	1	0	0	1	0	0
	All	42	1	0	11	2	1
70 and over	A	5	0	0	0	0	0
	B	13	3	2	4	2	0
	C	7	4	4	4	2	1
	D	5	3	2	0	0	0
	All	30	10	8	8	4	1
All	All	85	12	8	24	7	3
All	A + B	67	5	2	17	5	2
— 69	All	55	2	0	16	3	2

Maximum dimension of primary lesion group A less than 1 0 cm group B 1 0—1 9 cm group C 2 0—2 9 cm group D 3 0 cm and greater

years and 6 months and 17 years and 5 months after treatment were all described as edge recurrences

The results concerning the influence of age at treatment and of the size of the lesion on the frequency of recurrences and of fatal recurrences are shown in Table 4 for the four schemes of fractionation It is clear that the best results, with the lowest frequencies of recurrence, have been obtained with scheme 5 002, especially for the smaller lesions (groups A and B) and for patients under the age of 70

Table 4 *(cont.)*

Age at treatment (years)	Groups	Schemes of fractionation *(cont.)* 3 004 Net number	Number of recurrences	Number of fatal recurrences	2 005 Net number	Number of recurrences	Number of fatal recurrences
Less than 50	A	2	0	0	0	0	0
	B	3	1	0	3	1	0
	C	1	0	0	0	0	0
	D	0	0	0	0	0	0
	All	6	1	0	3	1	0
50—69	A	5	2	0	7	1	0
	B	7	0	0	18	5	2
	C	2	2	0	3	3	2
	D	2	0	0	2	1	1
	All	16	4	0	30	10	5
70 and over	A	0	0	0	1	1	0
	B	2	1	1	8	5	1
	C	0	0	0	3	1	1
	D	2	1	1	3	1	0
	All	4	2	2	15	8	2
All	All	6	7	2	48	19	7
All	A + B	19	4	1	37	13	3
—69	All	22	5	0	33	11	5

There were no recurrences among the 19 patients with group A lesions of maximum dimension less than 1.0 cm treated with scheme 5.002; there were in fact two recurrences though no fatal recurrences among the eight group A patients treated with scheme 2.005 and two non-fatal recurrences among the seven group-A patients treated with scheme 3.004 but no recurrences among the four group A patients receiving scheme 4.003.

However it is important to note that the advantage of scheme 5.002 is lost for patients aged 70 and over except for the smallest lesions of maximum dimension less than 1.0 cm. For the other three schemes the results are obviously worse than those for 5.002 and for patients under 70 the results appear to

Table 5

Sites and numbers of recurrences within 5 years for cases treated 1946—1959 — The numbers of fatal recurrences are given in brackets

Site of recurrence	Scheme of fraction				All schemes
	5 002	4 003	3 004	2 005	
Regional lymph nodes (glands)	9 (6)	4 (2)	4 (2)	12 (5)	29 (15)
Edge of treated field	1 (1)	2 (1)	3	5 (1)	11 (3)
Residual tumour in treated field	2 (1)	—	—	—	2 (1)
Area adjacent to treated field	—	*1*	—	*1*	2
Spread to alveolus	—	—	—	1 (1)	1 (1)
All sites	12 (8)	7 (3)	7 (2)	19 (7)	45 (20)

become progressively worse for schemes 4 003, 3 004 and 2 005 The greatest differences are observed between the results of schemes 5 002 and 2 005

More precise considerations are necessary The most important differences between the 5 year recurrence rates for the different schemes of fractionation are summarized in Table 6 The statistical analysis shows that all these differences appear to be either highly significant or significant This conclusion assumes the absence of serious systematic error It is clear that scheme 5 002 gives much better results than scheme 2 005 especially for patients under the age of 70 and for the smaller lesions It is interesting to note that there were no fatal recurrences in patients under the age of 70 who were treated initially with scheme 5 002

The sites of the recurrences, and of the fatal recurrences within 5 years, for the different schemes of fractionation are summarised in Table 5 The frequency of edge recurrence appears to be lower for scheme 5 002 than for all the other groups taken together but the difference is not significant statistically The edge recurrences were treated by excision, roentgen therapy or radon seed implant Metastases in regional lymph nodes were the commonest site of recurrence and about half of these proved fatal No significant difference in the frequency of lymph node recurrences is apparent for the different schemes of fractionation It may be mentioned that lymph node recurrences were treated by block dissection, if operable, with post operative roentgen therapy in some cases, and otherwise by roentgen therapy alone

Although not primarily the concern of this investigation it is of interest to consider briefly the 5 year survival rates for treatment with all schemes of fractionation For the selected patients in the whole series, the crude survival rate was 163/215 = 75 8 % and the net survival rate 163/183 = 89 1 % For the stage I cases (groups A and B), the net survival rate was 132/140 = 94 3 %

Table 6

Differences between the 5-year recurrence rates for the different schemes of fractionation

Method of estimation	Ages	Size of lesion	Schemes of fractionation compared	Recurrence rates numbers and approximate percentages		χ	P for 1 d f
Crude 5-year recurrence rate	All	All groups	5 002 v 2 005	12/101 v (11 9 %)	19/53 (35 9)	10 97	0 001
Net 5 year recurren e rate	All	All groups	5 002 v 2 005	12/85 v (14 1)	19/48 (39 6)	9 752	0 0016
			5 002 v 2 005 + 3 004	12/85 v (14 1 %)	26/74 (35 1)	8 489	0 0037
			5 002 v 2 005 + 3 004 + 4 003	12/85 v (14 1)	33/98 (33 7 %)	8 366	0 004
	— 69	All groups	5 002 v 2 005	2/55 v (3 6 %)	11/33 (33 3)	12 19	0 0007
(F tal recurrences only)	— 69	All groups	5 002 v 2 005	0/55 v	5/33 (15)	6 233	0 0125
	All	Groups A and B only (tage I)	5 002 v 2 005	5/67 v (7 5)	13/37 (35 1)	10 89	0 001

All these d fferences appear to be highly s gn ficant or s gnificant statist cally

Discussion

The evidence shows a substantial advantage of fractionation scheme 5 002 over the other schemes especially 2 005 for the same total minimum tumour dose of 3 750 R delivered in seven equal fractions in the overall time 8 days This level of minimum tumour dose is not high but apparently rather critical in that changing the scheme of fractionation from 5 002 reduces the therapeutic effectiveness of the same total dose of roentgen radiation It has not been possible to find any source of systematic error it appears reasonable and justifiable to apply the χ^2 test with Yates correction for continuity in the statistical tests of significance for 2×2 contingency tables (FISHER and YATES 1948 p 4) The differences summarised in Table 6 are in general large and must be regarded as showing that the advantage of scheme 5 002 over scheme 2 005 is highly significant statistically

It is relevant to comment that quite apart from differences between the results for the different schemes of fractionation, the results obtained for the

treatment of the whole series are relatively good and are comparable with published results, e g EBENIUS 1943, PATERSON, TOD & RUSSELL 1950, OESER 1954, COCCHI & HAAB 1960, BARTH & KERN 1961, LARSSON et coll 1963, MACKAY & SELLERS 1964 Strict comparison is almost impossible, because of the selection of cases in the present investigation

It is not yet possible to give a detailed explanation of the effects of fractionation observed The loss of the advantage of scheme 5 002 in patients aged 70 and over, except for the smallest lesions, suggests the possibility that reactions of the host tissues may play a part in the therapeutic response This finding probably supports the view that the advantage of scheme 5 002 depends at least in part on the vascular reaction produced by the first five fractions of the roentgen therapy and the resulting increase in the oxygen tension in the tumour Such an increase in oxygen tension after radiotherapy has been demonstrated in a number of superficial tumours by CATER & SILVER (1960) by means of oxygen cathode measurements, though it must be emphasized that the schemes of fractionation under consideration were not investigated Although such an explanation is plausible, it is impossible at the present time to estimate its quantitative importance It is suggested that it is still necessary to consider the part played by recovery processes in the tumour cells after irradiation

Conclusions

The main conclusion is that, for the cases of histologically verified squamous carcinoma of the lower lip in men investigated in this retrospective study, the scheme of fractionation 5 002 gives the best results for the standard total *minimum tumour dose of 3 750 R delivered in 7 equal fractions in* the overall time of 8 days The advantage of scheme 5 002 is lost for patients aged 70 and over, except for the smallest lesions of maximum dimension less than 1 0 cm From the practical point of view, it is recommended that the technique of 8 day roentgen therapy described should be used only with the scheme of fractionation 5 002

This investigation provides evidence for the existence of optimal conditions of fractionation in roentgen therapy at the appropriate level of dose Much further study of this problem is desirable

Acknowledgements

The authors wish to thank Miss R D Saunders formerly physicist at the Radiotherapeutic Centre Addenbrooke s Hospital for drawing attention to the apparent advantage of the scheme of fractionation described as 5 002

SUMMARY

A detailed account is given of a retrospective study of the influence of fractionation on the results obtained with a particular technique of roentgen therapy This work is based on the treatment in the years 1946—1959 inclusive of 215 cases of histologically verified primary squamous carcinoma of the lower lip in men There is evidence of large and statistically significant differences between the results obtained by different schemes of fractionation with the same total minimum tumour dose and the same overall time of treatment

ZUSAMMENFASSUNG

Auf Basis einer retrospektiven Untersuchung wird uber den Einfluss der Fraktionierung bei Röntgentherapie mittels einer speziellen Technik berichtet Das Material umfasste 215 Manner mit histologisch bestatigten squamosen Karzinomen der Unterlippe die in den Jahren 1946 bis 1959 einschliesslich behandelt wurden Bei Anwendung derselben totalen minimum Tumor Dosis und derselben Gesamtbehandlungszeit wurden grosse und statistisch signifikante Differenzen zwischen den Resultaten bei der Verwendung von verschiedenen Fraktionierungsschemas festgestellt

RÉSUMÉ

Les auteurs présentent en détail une étude rétrospective sur l influence du fractionnement sur les résultats d une technique de roentgen thérapie Ce travail est basé sur le traitement de 215 cas histologiquement vérifiés d épithélioma épidermoide différencié primitif de la levre inférieure chez des hommes de 1946 a 1959 inclusivement Cette étude demontre des différences importantes et statistiquement significatives entre les résultats donnés par différents types de fractionnement comportant la même dose minimale totale à la tumeur et la même durée totale de traitement

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FROM THE RADIOTHERAPY CLINIC (DIRECTOR PROF S MUSTAKALLIO) UNIVERSITY CENTRAL HOSPITAL, HELSINKI FINLAND

SPLIT COURSE RADIOTHERAPY OF CANCER

by

LARS R HOLSTI

Split course radiotherapy represents one form of periodic treatment and is divided into two or perhaps more phases separated by a rest interval The most important theoretical basis of the method consists of the differences in cell population kinetics between normal and malignant tissues The recovery of tumour cells during the rest interval is much slower than that of normal proliferating cells this gives time for normal tissues such as the skin to recover whereas very little if any restoration occurs in the tumour tissue In clinical practice the rest interval is extremely welcome to the patients and gives them a chance of improving their general condition

The present study was started in July 1963 and its background has been described elsewhere (HOLSTI 1966 HOLSTI & TASKINEN 1964) The aim of this paper is to report the experiences and results in the selected part of the material after 1 to 2 years follow up

Material The series consisted of 184 lung cancer cases 87 cases of cancer of the esophagus 46 cases of cancer of the oral cavity and 33 cases of cancer of the urinary bladder treated between July 1963 and September 1964 All

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Table 1

Clinical spread and histologic types in cases of carcinoma of the lung

Clinical spread	Split course treatment	Continuous treatment
No metastases	68	37
Intrathoracic spread	37	13
Supraclavicular nodes	13	3
Distant metastases	12	1
	Total 130	54
Type of tumour		
Squamous cell carcinoma	49	20
Undetermined carcinoma	13	7
Small cell carcinoma including oat cell carcinoma	24	6
Anaplastic carcinoma	24	12
Adenocarcinoma	4	2
Alveolar cell carcinoma	1	1
Cytology only	15	6
	Total 130	54

the 350 cases were histologically verified A total of 204 cases were treated with the split course technique, 130 of them had cancer of the lung, 38 cancer of the esophagus, 23 cancer of the oral cavity and 13 cancer of the urinary bladder The remaining 146 cases were treated continuously during the same time All the therapeutic courses refer to management of the primary tumour In addition to the above, a number of cases of carcinoma of the oropharynx or laryngopharynx have been treated with the split course technique but these will be reviewed later (HOLSTI & TASKINEN, to be published)

Methods The radiation therapy in cancer of the lung was administered by a 3 000 Ci cobalt unit or 35 MeV betatron from two or three fixed fields The esophageal carcinomas were usually treated by pendulum cobalt tele therapy, in six cases with 33 MeV photons Cancer of the bladder was regularly treated with cobalt teletherapy either from fixed fields or by pendulum therapy Carcinoma of the oral cavity (tongue and mouth) was treated in 19 cases with cobalt teletherapy, in 17 cases 20 MeV electrons were used and in 10 cases conventional roentgen 250 kV, HVL 1 0 mm Cu The daily tumour dose for roentgen and cobalt teletherapy averaged 150 to 170 R, and for betatron therapy with 33 MeV photons and 20 MeV electrons it was 170 to 200 R The treatment planning was identical in both the continuous and split

Table 2

Results of treatment in cases of carcinoma of the lung

Treatment	Time of survival			Recurrence free
	6 months	1 year	2 years	1 year
Split course	91/130 (70)	46/130 (35)	5/51	37/130 (28)
Continuous	29/54 (54)	18/54 (33 ,)	1/27	15/54 (27)

course treatment groups The treatment volume in pulmonary carcinoma normally included the mediastinum Treatment was given 6 times weekly

The treatment in the split course groups was interrupted for two and some times three weeks (average 16 to 17 days) in the middle of the course of treat ment independently of the response and reaction to therapy After the inter val, treatment was continued with roughly the same dose The mean total minimum tumour dose was 5 500 to 6 000 R in carcinoma of the lung and urinary bladder 5 700 to 6 300 R in the treatment of esophageal cancer in cancer of the oral cavity 5 300 R with cobalt teletherapy and 6 200 R with electron therapy The mean treatment time in split course therapy was 7 to 8 weeks the doses being 5 to 10 per cent higher than in the continuous treat ment The majority of the cases were of out patients who went home for the rest interval The patients general condition blood values and the clinical and roentgenologic condition of the tumour were followed

Selection of cases The selection of cases in the groups of the present material was not truly at random the author included his cases in the split course group whereas the other therapist placed his cases on continuous treatment No restrictions were imposed in this material in regard to patient s age and spread of the tumour All the cases considered suitable for radiotherapy were accepted for both split course and continuous treatment A critically ran domised clinical trial was started in October 1964

Results

Carcinoma of the lung The cases are classified by clinical spread and histo- logic distribution in Table 1 which shows that there are no striking differences in the composition of the therapeutic groups The sub group with no detectable metastases on admission was the largest in both therapeutic groups squamous cell carcinoma accounted for 37 per cent of the histologic types in both of them The continuous group included slightly fewer small cell carcinomas

Table 3

Clinical classification of the cases of carcinoma of the esophagus

Clinical spread	Split course (total 38)	Continuous (total 49)
No metastases	32	43
Mediastinal spread	2	4
Supraclavicular nodes	3	1
Distant metastases	1	1

Table 4

Results of treatment in carcinoma of the esophagus

Treatment	Survival rates			Recurrence free
	6 months	1 year	2 years	1 year
Split course	30/38 (79 %)	13/38 (34 %)	0/9	9/38 (24 %)
Continuous	28/49 (57 %)	9/49 (18 %)	4/34	8/49 (16 %)

than the split course group The survival rates after 6 months, 1 year and 2 years, respectively, are compared in Table 2 The percentage of survivors in the split course group was higher after 6 months but there was no difference in the 1 year survival rates The material followed for 2 years is still small The percentage of recurrence free cases during the first year was the same as in the continuously treated group Earlier, in a smaller pulmonary carcinoma material (HOLSTI 1966), the results appeared to be better for patients given split course rather than continuous therapy although even in that material the difference was not statistically significant

Carcinoma of the esophagus The clinical classification of the material is given in Table 3 Local tumours were most numerous in both therapeutic groups Gastrostomy was performed in five cases in the split course series and in four cases in the continuous series The therapeutic results in Table 4 indicate that both the 6 month and 1-year survival rates were a little higher in the split course group, no differences had been revealed earlier (HOLSTI 1965 1966) The number of recurrence free cases after a year was also slightly greater in the split course group

Carcinoma of the oral cavity The following anatomical sites were included the mobile portion of the tongue, the floor of the mouth, the buccal mucosa, the lower gingiva, the upper gingiva, and the hard palate The definitions

Table 5

Number of cases treated for carcinoma of the oral cavity classified in stages according to the TNM system

Stage	Split-course (total 23) N	N	N	N	Continuous (total 23) N	N	N	N
T	4	1	—	—	7	1	—	—
T	8	2	—	1	7	1	—	—
T	6	1	—	—	4	—	—	3
T_4	—	—	—	—	—	—	—	—

Table 6

Results of treatment in carcinoma of the oral cavity

Treatment	Survival rates 6 months	1 year	2 years	Recurrence free 1 year
Split-course	21/23	16/23 (70 %)	1/5	8/23 (35 %)
Continuous	20/23	14/23 (61 %)	5/16	8/23 (35 %)

conform to those given by FLETCHER & MACCOMB (1962) The split course group comprised 15 carcinomas of the tongue and 8 of the mouth while the continuous group included 11 growths of the tongue and 12 of the mouth The cases are classified according to the TNM system in Table 5 The continuous group included a slightly higher number of T_1 cases but the distribution was otherwise fairly even between the therapeutic groups The number of cases on split course therapy that survived for a year was slightly greater than the corresponding survivors receiving continuous therapy (Table 6) On the other hand no definite difference was seen in the 6 month and 2 year results However the material followed for two years is still too small to warrant conclusions The number of recurrence free cases one year after therapy was exactly the same in both the therapeutic groups

Carcinoma of the bladder The distribution of the material by the TNM system is given in Table 7 The split course group contained a great number of un operated T_3 cases but the continuous treatment group included six resected cases of T_2 which were not found at all in the split course series The split course group cannot consequently be regarded as more favourable prognos tically than the continuous group The therapeutic results appeared to be distinctly superior in the split course group after the short observation period (Table 8) but this must be regarded as only a preliminary result The number

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Continuous	28/49 (57 %)	9/49 (18 %)	4/34	8/49 (16 %)

than the split course group The survival rates after 6 months, 1 year and 2 years, respectively, are compared in Table 2 The percentage of survivors in the split course group was higher after 6 months but there was no difference in the 1 year survival rates The material followed for 2 years is still small The percentage of recurrence free cases during the first year was the same as in the continuously treated group Earlier, in a smaller pulmonary carcinoma material (HOLSTI 1966), the results appeared to be better for patients given split course rather than continuous therapy although even in that material the difference was not statistically significant

Carcinoma of the esophagus The clinical classification of the material is given in Table 3 Local tumours were most numerous in both therapeutic groups Gastrostomy was performed in five cases in the split course series and in four cases in the continuous series The therapeutic results in Table 4 indicate that both the 6 month and 1 year survival rates were a little higher in the split course group, no differences had been revealed earlier (HOLSTI 1965, 1966) The number of recurrence free cases after a year was also slightly greater in the split course group

Carcinoma of the oral cavity The following anatomical sites were included the mobile portion of the tongue, the floor of the mouth, the buccal mucosa, the lower gingiva, the upper gingiva, and the hard palate The definitions

proliferation (TEIR 1961) Since there is no evidence that homeostatic mechanisms speed up the growth rate of malignant cells after radiation damage, tumour cells compared with normal epithelial cells will recover very slowly In addition, irradiation causes mitotic suppression which may last several days even weeks Hence, during the rest interval in split course therapy there is proliferation of normal cells but the recovery if any of the tumour tissue is slow HANKS & KAPLAN (1965) found little or no recovery in radiation induced lymphosarcoma of mice, and suggested that if human lymphocytic tumours were similar they might best be treated by spaced fractionated radiotherapy For most tumours the volume or cell population doubling time lies between some weeks and several months (SPRATT & SPRATT 1964 BRENNER et coll) The renewal time for normal epidermal and epithelial cells on the other hand is very short, i e only a few days (VON BERTALANFFY 1960) The interval in split course therapy must naturally be shorter than the doubling time of the tumour treated

Clinical observations by SAMBROOK (1962) SCANLON (1963) and HOLSTI (1966) have shown regression of the tumour during the interval and sometimes even its complete disappearance This was established also in the present material especially in the oral cavity and the bladder when the tumour was seen by the naked eye A dose of 3 000 R may in fact suffice in radiosensitive tumours to cause the disappearance of the tumour macroscopically The questions of the optimal length of the interval and the optimal time at which it should be begun require more study Local reactions reflecting radiation damage take 2 to 3 weeks to develop The response of reparative proliferation seems to be maximal between the 4th and 7th week after beginning of each course of radiation (SAMBROOK 1964) in other words 2 to 5 weeks after beginning of the interval

Experiments in vitro have shown that a certain repair of the radiation damage provoked under aerobic conditions occurs but no such repair related to cellular reproduction appears to occur after irradiation performed in anoxic conditions (REVESZ & LITTBRAND 1965 LITTBRAND & REVESZ 1964) If these observations possess general validity there is a conceivable advantage when irradiating a hypoxic tumour in well oxygenated surroundings in the use of small radiation doses to avoid the therapeutically untoward oxygen effect (RÉVESZ & LITTBRAND) The good results obtained by ultra fractionated radiotherapy (BACLESSE 1958 1964) may perhaps be explained in this way It is equally possible that the problem of hypoxia can be overcome partly through split-course therapy In the light of the results obtained by REVESZ s research team it seems that the split course technique may be especially suitable for the management of hypoxic or anoxic tumours since no repair

Table 7

Number of cases treated for carcinoma of the bladder classified in stages according to the TNM system

Stage	Split course group (13 cases)	Continuous treatment (20 cases)
T_1	—	—
T_2	9	5 (one resected)
T_3	2	6
T_4	2	10 (six resected)

Table 8

Results of treatment in cancer of the bladder

Treatment	Survival rates			Recurrence free
	6 months	1 year	2 years	1 year
Split course	12/13	11/13 (85 %)	2/4	9/13 (69 %)
Continuous	16/20	10/20 (50 %)	4/16	7/20 (35 %)

of recurrence free cases was also distinctly higher in the split course than in the continuous treatment group Cystoscopy was performed in the bladder cases prior to treatment, often half way through treatment and regularly at 3 month intervals afterwards

In all the four cancer series, when the patients returned from the interval in treatment, their general condition had improved, the blood values were better and symptoms caused by irradiation, such as dysphagia and irradiation cystitis, had disappeared, the appetite had improved and the state of mind was cheerful

Discussion

Cell population kinetics plays an important role in the response of tissues to irradiation Theoretically, split course therapy is based on the differences in cell kinetics between normal and malignant cells Recent observations by MENDELSOHN (1965) on animal tumours suggest that tumours of common origin have common cell cycles and that the cycle in the tumour may be very different from that in the tissues of origin The most important kinetic property of malignant tumours is that their proliferative activity is not controlled by any homeostatic mechanism Cell proliferation and cell loss are balanced in normal cell populations and they have a compensatory homeostatic mechanism that stimulates reparative proliferation Destroyed cells also stimulate

interval Furthermore therapeutic reactions such as dysphagia mucosal re actions irradiation cystitis, and the like disappear during the rest interval and treatment can be begun anew, as it were from the beginning Marked regression of the tumour is oft n observed after the rest interval The utilisation of the differential repopulation rate in normal and tumour tissue in split course therapy is a sound philosophy (Fowler 1966) although we need more radiobiologic and clinical facts for further development of the method

SUMMARY

The results of split-course radiotherapy in 204 ca s of cancer of the lung esophagus oral cavity and urinary bladder were compared with those in 146 continuously treated cases The results were no worse when conventional continuous therapy was abandoned and replaced by split-course therapy with a rest interval half way through the treatment

ZUSAMMENFASSUNG

Die Endresultate bei unterbrochener Serienbestrahlung in 204 Fallen von Krebs in Lungen Speiserohre Mundhohle und Harnblase wurden mit den Resultaten einer fortlau fenden Strahlenbehandlung von 146 Fallen verglichen Die Resultate waren keineswegs schlechter wenn statt der orthodoxen kontinuierlichen Behandlung fraktionierte Radiothera pie mit einem Intervall mitten in der Behandlungsperiode gegeben wurde

RESUME

Les résultats de la radiothérapie fractionnée dans 204 cas de cancer du poumon de l oeso phage de la cavité buccale et de la vessie sont comparés avec ceux de 146 cas traités d une façon continue Les résultats ne sont pas pires quand on abandonne le traitement continu classique et qu on le remplace par le traitement fractionné avec un intervalle de repos au m lieu du traitement

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can occur in them during the relatively short rest interval On the other hand, the vascular reaction and hyperemia caused by the irradiation will increase the oxygen tension in tumour tissues (CATER & SILVER 1960), the increase is not statistically significant though (EVANS & NAYLOR 1963) The significance of this reaction during the rest interval is consequently uncertain

Skin regeneration occurs in the course of ultra fractionated radiotherapy and the skin reactions may even heal during the treatment (SAMBROOK 1963) There is an increase in the therapeutic ratio due to the differences between the kinetics of normal and malignant cells A similar gain in the therapeutic ratio is achieved in a different way by recourse to the split course technique

The results obtained for the present material in cancer of the esophagus and of the oral cavity show a slightly higher and for cancer of the urinary bladder a clearly higher survival rate in the split course group The treatment techniques made no difference to the survival rate in the pulmonary carcinoma series Non metastasising tumours are most suitable for split course therapy The results do not warrant any other conclusion in this phase, except that when the split course technique is employed with a total dosage practically the same as that used normally, the results are no worse than those achieved with conventional continuous therapy This confirms opinions presented earlier (SAMBROOK 1964, SCANLON 1965, HOLSTI 1966) To compensate for the interval, a very small increase in dose is required (DUSAULT 1964) It should be increased by about 10 per cent at the 5 000 to 6 000 R level, as was done for part of the present material It is uncertain whether the rest interval itself is enough to improve the therapeutic results appreciably but the split course techniques permits increasing the total dosage to 7 000 to 8 000 R even with the 250 kV technique (SAMBROOK 1964, SCANLON 1963) Hence, if the possibilities offered by the split course technique are to be effectively exploited, the overall dosage should be raised appreciably It is disadvantageous to begin the rest interval at the outset of the therapeutic course (DUSAULT 1964) Until more facts are available, it would seem advisable to have the interval always after 2 500 to 3 000 R, in other words, once half way through the treatment when the conventional total dosage is given, and twice when high total dosages are in question

To conclude, it is not possible on the strength of the present work to give a definitive answer to the question whether split course produces better results than continuous therapy But it is evident that the results are no poorer with split course than with continuous radiotherapy, and this is a very important point The clinical advantages are patients tolerate radiotherapy much better when it is divided into phases Their general condition, blood values and state of mind are considerably improved when they return from the rest

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LA CASTRATION DANS LE CANCER DU SEIN CHIRURGIE OU RADIATIONS

par

C M LALANNE P JURET F HOURTOULE et D SARRAZIN

Le but de ce travail est de discuter les techniques et non les indications de la castration chez les femmes atteintes de cancer du sein A l Institut Gustave Roussy (2 7) il a été decide en 1957 de castrer systematiquement toutes les malades réglées et celles dont les dernieres regles remontent a moins de deux années Cependant les malades operees d emblee qui ne presentent pas d envahissement ganglionnaire apres un examen histologique soigneux des ganglions (N) ne subissent pas de castration

Les resultats observés chez les malades traitees de cette façon entre 1957 et 1962 justifient cette attitude (Tableau 1) Les taux de survie a 3 ans des malades de moins de 50 ans, c est à dire susceptibles de beneficier de la castration apparaissent améliorées par rapport a ceux des malades correspondantes de la période précédente (1954—1956) qui n ont pas ete castrees Ceci est valable aussi bien pour les malades operees d emblée que pour les malades opérées après radiothérapie En fait pour ces dernieres l amelioration constatée est probablement en partie liée a la telécobalt thérapie qui a éte introduite en meme temps que la castration dans le protocole thérapeutique (8) Ces résultats apportent donc une confirmation aux essais thérapeutiques

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Tableau 2

Comparaison de la moyenne des poids (en mg) des cornes utérines des souris injectées avec l'urine des malades castrées par la chirurgie ou par les radiations au 2e et au 6e mois suivant la castration

Délai après castration	Castration	Dilution au 1/200	Dilution au 1/100	Dilution au 1/50	Dilution au 1/25
2e mois	Ovariectomie	7,5	12,9	16,7	21,3
	Irradiation	8,7	12,4	17,2	22,4
	Signification (S < 0,05)	Non	Non	Non	Non
6e mois	Ovariectomie	8	9,9	13,5	20
	Irradiation	8,3	14,3	19,5	23,1
	Signification (S < 0,05)	Non	Oui	Oui	Non

pour cette comparaison. Elles ont été divisées au hasard en deux groupes, l'un correspondant aux malades nées une année impaire castrées par les radiations (19 malades), l'autre correspondant aux malades nées une année paire castrées par la chirurgie (15 malades). Le taux des gonadotropines a été mesuré 2 et 6 mois après la castration. Les urines des malades étaient recueillies pendant 24 heures. Des fractions de ces urines convenablement diluées étaient injectées à des souris impubères. Leur teneur en gonadotropines était appréciée au moyen du poids des cornes utérines des animaux (Tableau 2).

Les deux techniques, radiothérapie ou chirurgie, sont très proches l'une de l'autre. Au 2e mois il n'y a aucune différence statistiquement significative. Par contre, au 6e mois il apparaît un avantage en faveur de la castration par les radiations, au moins pour deux des dilutions (au 1/100 et au 1/50) sur les quatre qui ont été testées. Tout se passe comme si entre le 2e et le 6e mois le taux des gonadotropines continue à augmenter chez les femmes irradiées alors qu'il tend à diminuer chez les ovariectomisées. En d'autres termes, la dépression des oestrogènes serait plus profonde et plus prolongée après l'irradiation qu'après l'exérèse des ovaires. Si l'on se fie aux dosages des gonadotropines tels qu'ils ont été pratiqués par notre groupe, cette expérimentation fait donc ressortir une supériorité de la technique radiologique sur la technique chirurgicale. Ce résultat, de prime abord paradoxal, est difficile à expliquer. Deux hypothèses cependant peuvent être avancées.

La première reposerait sur l'existence chez certaines malades de tissu ovarien accessoire situé dans le pelvis en dehors des ovaires proprement dit; ce tissu laissé en place par le chirurgien rétablirait la fonction ovarienne après l'ova

Tableau 1

Survie a 3 ans des malades atteintes de cancer du sein (après exclusion des malades présentant des métastases a distance au depart et des N) en fonction de l association systématique de la castration au traitement locorégional chez les femmes de moins de 50 ans

	Nombre total	Nombre vivant a trois ans	Pourcentage vivant à trois ans
Pas de castration (1954—1956)	107	61	57
Castration (1957—1962)	149	109	73

menés par PATTERSON & RUSSELL (1959) et NISSEN MEYER (1964), concluant a l'efficacité de la castration D'ailleurs, NISSEN MEYER n'hésite pas à étendre les indications de la castration bien au delà de la ménopause Pour etre complet a propos des resultats de notre Institut, il faut signaler enfin que le taux de survie a 5 ans s'élève a 91 % chez les malades qui n ont pas de ganglions envahis (N) et qui, pour cette raison, n'ont pas reçu de traitement complémentaire (13)

Une fois admis le principe de la castration, celle ci peut etre réalisée par deux moyens l ovariectomie ou l'irradiation Dans une premiere période, nous avions choisi l'ovariectomie que nous considérions comme plus sure et peut-etre plus efficace Par la suite, la difficulté de faire accepter une nouvelle intervention chirurgicale a des malades convalescentes d'une mastectomie et les résultats apparemment satisfaisants obtenus par d'autres auteurs au moyen de la castration par les radiations, nous ont fait remettre en question cette préference chirurgicale Finalement, pour étayer notre choix sur des donnees objectives, nous avons effectue une comparaison biologique statisti quement controlee entre l'irradiation ovarienne et l ovariectomie bilaterale

1 Comparaison biologique ovariectomie/irradiation ovarienne

Il aurait ete trop long de tester les deux techniques en fonction de leur effet sur l évolution du cancer Il a donc éte décide d'utiliser comme critere de comparaison la quantite de gonadotropines excrétés dans l'urine (HMG ou HGP) Ce taux est d autant plus elevé que l imprégnation oestrogenique est plus faible, donc que la suppression de la fonction ovarienne par la castra tion est plus complete

La technique de dosage des gonadotropines et l'analyse statistique des resultats ont éte exposes dans un autre travail (4) Nous rappellerons simple ment ici que ce sont les malades operables d emblee qui ont été retenues

Tableau 2

Comparaison de la moyenne des poids (en mg) des cornes utérines des souris injectées avec l'urine des malades castrées par la chirurgie ou par les radiations au 2e et au 6e mois suivant la castration

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riectomie , par contre, il serait, comme les ovaires, stérilisé par l'irradiation globale du pelvis, telle qu'elle est pratiquée pour obtenir la castration On pourrait aussi invoquer le role de tissu surrénalien aberrant situé dans le pelvis et dont l'irradiation serait faite en meme temps que celle des ovaires

La seconde hypothese, plus problématique, tirerait argument de la sélec tivité de l'irradiation En effet, celle ci est pratiquée à des doses qui arretent de façon definitive l'évolution des follicules vers la maturation, mais qui respectent les autres éléments constituant l'ovaire Ceux ci interviennent peut etre dans l'équilibre régnant entre l'ovaire et les autres glandes endocrines, comme l'hypophyse ou les surrénales L'action des radiations ne portant que sur quelques cellules particulieres et épargnant le reste de l'ovaire ainsi que ses connexions, sa sélectivité anatomique se retrouverait au niveau physio logique, ou elle resterait centrée sur le tarissement des œstrogènes Au con traire, la suppression de l ensemble du tissu ovarien et la rupture de ses con nexions avec le reste de l'organisme par l ovariectomie entraîneraient des per turbations non sélectives Ainsi les variations pondérales des cornes utérines de souris sont fonction de l'activité FSH et de l'activité ICSH des urines des malades Mais l'activité ICSH parait prépondérante et l on ignore si les deux activités varient de façon parallèle ou divergente selon qu'on utilise l une ou l'autre méthode de castration De plus, les perturbations créées par l ovariectomie sont immédiatement plus profondes que celles liées à l irradia tion et provoquent un déficit hormonal que l on peut croire d'emblée total De ce fait, elles sont sans doute susceptibles de susciter des phenomenes de *compensation plus précoces et plus accentués au niveau d'autres glandes,* comme la surrénale La réponse aux deux techniques serait donc encore plus dissemblable, si l'on tient compte du facteur temps la chirurgie ayant une action non seulement totale, mais immédiate et brutale , l irradiation ayant une action non seulement sélective, mais aussi progressive et plus physio logique

Certes, l insuffisance de ces hypothèses ne saurait échapper Et il faut sou haiter que de nouveaux travaux viennent apporter des éclaircissements sur les mécanismes mis en jeu et sur leur chronologie

Quoi qu'il en soit, le fait demeure que dans cette comparaison, l irradiation ovarienne provoque une dépression de l imprégnation œstrogénique plus complete que l ovariectomie bilatérale D ailleurs cette notion n est pas en réalité aussi paradoxale qu il y parait à première vue Certains travaux antérieurs avaient déjà remis en cause la supériorité de l ovariectomie, en particulier, celui, tres intéressant, de DICZFALUSY et coll (1959) Ces auteurs ont d'abord pratiqué une irradiation ovarienne chez 17 femmes Cinq mois plus tard, ils pratiquaient une ovariectomie chez ces memes malades Les

Tableau 3

Castration chirurgicale — Fréquence et survie à 5 ans des malades atteintes de cancer du sein avec métastases ovariennes

Catégories de malades	Total	Chirurgie d'emblée	Chirurgie après radiothérapie	Chirurgie impossible –	Antérieurement traités hors I G R
Nombre total castrées	148	52	47	17	32
Pourcentage avec métastases ovariennes	11	8	6	12	22
Pourcentage avec métastases ovariennes apparues à 5 ans sur le total des cas	1 3	2	2	0	0

mesures de l'excrétion des œstrogènes ont montré que le tarissement œstrogénique provoqué par l'irradiation n'était pas aggravé de manière significative par l'exérèse des ovaires. Cette dernière apparaissait en définitive incapable de faire mieux que l'irradiation antérieure. Objectivement, on dispose donc de deux études conduites selon des méthodes différentes et basées sur des tests différents dont les conclusions s'accordent pour reconnaître à la castration par les radiations une efficacité biologique au moins égale, sinon supérieure à celle de la castration par la chirurgie.

2 Comparaison clinique ovariectomie/irradiation ovarienne

Avant de choisir entre les deux techniques il importait de rechercher si cette équivalence se retrouverait sur le plan clinique.

Du point de vue cancérologique NISSEN MEYER a testé sous la forme d'un essai thérapeutique l'influence respective de chacune des deux techniques sur le pronostic d'un groupe de malades pré-ménopausées, dont la plupart était au stade II avec envahissement axillaire et degré histologique élevé de malignité (9). Il n'a pas noté de différence statistiquement significative entre les deux techniques mais il réserve encore ces conclusions en raison des effectifs trop faibles comparés. A ceci on pourrait encore ajouter que les deux seuls essais thérapeutiques publiés attestant l'efficacité de la castration dans le traitement du cancer du sein, celui de PATTERSON & RUSSELL (1959) et celui précisément de NISSEN MEYER (1964) ont tous deux été réalisés avec des irradiations ovariennes.

riectomie ; par contre, il serait, comme les ovaires, stérilisé par l'irradiation globale du pelvis, telle qu'elle est pratiquée pour obtenir la castration. On pourrait aussi invoquer le rôle de tissu surrénalien aberrant situé dans le pelvis et dont l'irradiation serait faite en même temps que celle des ovaires.

La seconde hypothèse, plus problématique, tirerait argument de la sélectivité de l'irradiation. En effet, celle-ci est pratiquée à des doses qui arrêtent de façon définitive l'évolution des follicules vers la maturation, mais qui respectent les autres éléments constituant l'ovaire. Ceux-ci interviennent peut-être dans l'équilibre régnant entre l'ovaire et les autres glandes endocrines, comme l'hypophyse ou les surrénales. L'action des radiations ne portant que sur quelques cellules particulières et épargnant le reste de l'ovaire ainsi que ses connexions, sa sélectivité anatomique se retrouverait au niveau physiologique, où elle resterait centrée sur le tarissement des œstrogènes. Au contraire, la suppression de l'ensemble du tissu ovarien et la rupture de ses connexions avec le reste de l'organisme par l'ovariectomie entraîneraient des perturbations non sélectives. Ainsi les variations pondérales des cornes utérines de souris sont fonction de l'activité FSH et de l'activité ICSH des urines des malades. Mais l'activité ICSH paraît prépondérante et l'on ignore si les deux activités varient de façon parallèle ou divergente selon qu'on utilise l'une ou l'autre méthode de castration. De plus, les perturbations créées par l'ovariectomie sont immédiatement plus profondes que celles liées à l'irradiation et provoquent un déficit hormonal que l'on peut croire d'emblée total. De ce fait, elles sont sans doute susceptibles de susciter des phénomènes de compensation plus précoces et plus accentués au niveau d'autres glandes, comme la surrénale. La réponse aux deux techniques serait donc encore plus dissemblable, si l'on tient compte du facteur temps : la chirurgie ayant une action non seulement totale, mais immédiate et brutale ; l'irradiation ayant une action non seulement sélective, mais aussi progressive et plus physiologique.

Certes, l'insuffisance de ces hypothèses ne saurait échapper. Il faut souhaiter que de nouveaux travaux viennent apporter des éclaircissements sur les mécanismes mis en jeu et sur leur chronologie.

Quoi qu'il en soit, le fait demeure que dans cette comparaison, l'irradiation ovarienne provoque une dépression de l'imprégnation œstrogénique plus complète que l'ovariectomie bilatérale. D'ailleurs, cette notion n'est pas en réalité aussi paradoxale qu'il y paraît à première vue. Certains travaux antérieurs avaient déjà remis en cause la supériorité de l'ovariectomie, en particulier, celui, très intéressant de DICZFALUSY et coll. (1959). Ces auteurs ont d'abord pratiqué une irradiation ovarienne chez 17 femmes. Cinq mois plus tard, ils pratiquaient une ovariectomie chez ces mêmes malades. Les

théorique de cancérisation post radiothérapique existe il est en pratique très faible et il ne peut sérieusement retenir l'attention pour des malades déjà porteuses d'un cancer mammaire

Restent à considérer les conséquences fonctionnelles Les troubles de la ménopause sont de nature identique avec les deux méthodes Et ils ne paraissent pas plus sévères après la castration par les radiations (1) Il est possible même que les troubles de la sexualité soient un peu moins accusés après l'irradiation qu'après l'ovariectomie C'est du moins l'impression que KOTTMEIER (1964) a tiré de l'étude des ménopauses provoquées chez les femmes jeunes par la radiothérapie des cancers du col utérin Mais les facteurs psychologiques sont dans ce domaine extrêmement importants et rendent difficile toute évaluation objective

Enfin il faut en arriver à ce qui constitue habituellement l'argument majeur des partisans de l'ovariectomie ce sont les échecs observés après l'irradiation Celle ci ne provoquerait pas toujours la ménopause et même n'aurait pas empêché quelques femmes de mener à bien des grossesses A l I G R , nous n'avons pas observé d'échec parmi plusieurs centaines de malades irradiées Jamais il n'a été nécessaire de pratiquer une ovariectomie pour corriger l'inefficacité d'une irradiation Par contre nous avons souvenir de quelques cas exceptionnels il est vrai dans lesquels la persistance de menstruation après l'ovariectomie bilatérale a conduit notre endocrinologiste à demander une irradiation complémentaire Nous ne nous hasarderons pas à donner une interprétation de ces cas extrêmes Il suffit de les rapporter pour indiquer que l'intervention chirurgicale n'est pas toujours couronnée de succès D'ailleurs il est certain que les échecs observés après irradiation sont en grande majorité imputables non pas à la méthode mais à la technique utilisée par le radiothérapeute Cette dernière mérite donc quelques commentaires

3 Technique de la castration par les radiations

Les techniques rapportées dans la littérature sont surtout remarquables par leur diversité et parfois leur imprécision Nous ne nous attarderons pas à les passer en revue Nous nous bornerons plutôt à décrire la technique que nous utilisons à l I G R et qui nous a donné des résultats constants Trois paramètres entrent en jeu le volume irradié la dose et la durée de l'irradiation

Le volume irradié couvre l'ensemble du petit bassin Il déborde de 1 cm les rebords osseux droit et gauche au niveau de la plus grande largeur il s'appuie vers les pieds sur la symphyse pubienne et remonte vers la tête jusqu'au promontoire Ce volume est irradié au moyen de deux champs pelvien antérieur

Cependant, les données biologiques et cancérologiques ne sont pas les seules qui doivent etre prises en considération Meme a efficacité égale des deux méthodes, il faut faire intervenir dans leur comparaison d'autres facteurs significatifs pour le clinicien

En premier lieu, on peut mettre au passif de la chirurgie le risque de morta lite opératoire Mais ce risque a été pratiquement éliminé par les techniques modernes d'anesthésie et de réanimation, et surtout par une sélection soigneuse des malades qui sont soumises a l intervention A l'heure actuelle, il n'entre plus en ligne de compte Par contre, a l'actif de la chirurgie, on doit porter le fait qu'elle réalise l'exérese des métastases ovariennes occultes Cependant, chez les malades castrées a titre systématique, la fréquence des métastases ovariennes occultes est inferieure a 10 % (Tableau 3) et lorsque ces métastases existent, il est rarissime qu'elles soient isolees Elles temoignent presque tou jours d'une dissémination cancéreuse déja largement établie Comme l atteste l'évolution des malades qui en sont atteintes leur taux de survie a 5 ans ne represente que 1 % a 2 % du total des cas La suppression de la métastase ovarienne n'a donc sans doute par elle meme que peu d'effet sur le pronostic et ne constitue qu'un argument *négligeable en faveur* de la chirurgie Quant aux castrations faites a titre therapeutique chez des malades dont les lesions ont dépasse le stade loco régional, l exérese de la métastase ovarienne ne saurait évidemment revetir chez elles aucune signification therapeutique

A la radiothérapie, il faut reconnaitre plusieurs inconvénients La maladie des rayons ne peut etre sérieusement retenue les doses délivrees sont faibles et bien tolérees, malgre quelques troubles digestifs, en particulier des nausées qui cessent à la fin de l irradiation Il en est de meme du danger de ré chauffer une infection latente du pelvis Meme si ce danger existe réellement, les traitements anti infectieux actuels sont suffisamment actifs pour le con troler aisement

A t on le droit d'evoquer davantage le risque de cancerisation secondaire des organes irradiées et, en particulier, des ovaires dont on connait la sus-*ceptibilité dans ce domaine Le temps de latence considérable nécess*aire pour que le tissu irradié se cancérise et la simultanéite toujours possible d un cancer ovarien et d un cancer mammaire, genent pour mesurer ce risque Malgré ces difficultes, des enquetes basées sur des chiffres importants éliminent prati quement le danger de radiocancerisation secondaire (1, 6, 11, 12) Il n appa rait pas d'incidence significativement plus élevée de tumeurs du petit bassin chez les femmes irradiees que chez les autres Cependant, ces données statis tiques n'ont pas convaincu tout le monde, et certains auteurs font encore quelques réserves sur ce point Un doute persiste donc a ce sujet qui justifie de nouvelles investigations En fin de compte, on peut dire que, si le risque

4 Irradiation ovarienne contre ovariectomie

Il semble que les facteurs susceptibles d intervenir dans le choix entre la castration chirurgicale et la castration par les radiations ont maintenant ete passes en revue

1 Sur le plan biologique deux travaux concordants basés l un sur le dosage des œstrogenes (DICZFALUZY) l autre sur le dosage des gonadotropines (I G R) montrent que l irradiation est aussi et peut etre plus efficace que la chirurgie

2 Sur le plan cancerologique aucune preuve de la superiorite de l une ou l autre technique n a pu encore etre fournie (NISSEN MEYER)

3 Sur le plan clinique en l absence de données objectives et malgre les reserves faites plus haut le seul argument actuellement decisif reste que la radiotherapie apparait comme un moyen facile de provoquer la castration et de toute façon plus facile que l ovariectomie

Il faut reconnaitre en effet que l irradiation n entraine que peu de gene pour les malades Pour celles qui sont soumises a la radiotherapie post operatoire loco regionale les 5 ou 6 seances sur les ovaires passent aisement dans le cours du traitement Pour les autres celles qui ne sont soumises qu a la castration les 3 ou 4 seances reparties sur une duree toujours inferieure a une semaine sont habituellement pratiquees a titre ambulatoire Les inconvenients des quelques allees et venues qui sont ainsi imposees aux malades ne sauraient etre mis en balance avec ceux d une intervention chirurgicale qui exige une hospitalisation de plusieurs jours Cet avantage social se double d ailleurs d un avantage financier non negligeable l irradiation etant moins onereuse

En fin de compte c est sur cet argument de la commodite que nous avons a l I G R préferé depuis plusieurs annees l irradiation ovarienne puisque des tests differents biologiques cancerologiques ou cliniques ont ete jusqu a ce jour incapables de prouver la superiorite de l une ou l autre technique Il est bien entendu que nous restons prets a reviser notre position si cette preuve etait enfin apportee en faveur de la chirurgie D ailleurs cette attitude de principe en faveur de l irradiation demande a etre legerement nuancee

Il y a lieu de considerer en particulier les circonstances dans lesquelles est posée l indication de la castration La castration systématique qui est faite sur des malades ne presentant aucun symptome en quelque sorte dans un but prophylactique s accomode parfaitement de l irradiation et de son action differee Par contre la castration therapeutique réalisee chez des malades presentant du cancer en evolution souleve quelques problemes Il peut apparaitre utile en effet d obtenir une action rapide lorsque les lesions sont deja étendues lorsque le cancer s aggrave rapidement et surtout lorsqu il est

et pelvien postérieur, opposés Les champs mesurent 10 à 12 cm dans le sens tete-pied et 13 à 15 dans le sens transverse, selon la conformation des malades

La quantité de rayonnement administrée est calculée dans le plan frontal du pelvis L'etude de la répartition de la dose dans les tissus montre que cette repartition est à peu pres homogene entre les deux portes d'entrée avec le télecobalt que nous employons La repartition est peu differente avec les rayonnements classiques suffisamment filtrés (CDA 2 mm Cu), au moins pour les malades d'epaisseur inférieure à 22 cm Pour les autres, la technique peut etre modifiée (addition de deux champs latéraux) afin que les ovaires reçoivent bien la dose prévue et que la reaction cutanée reste acceptable

La dose et *l'étalement* dépendent l un de l'autre Ils diffèrent aussi selon que la castration est réalisée en meme temps qu'une irradiation post operatoire ou selon qu'elle est realisée seule

Dans le premier cas, il s'agit de malades qui viennent pendant 4 à 5 semaines dans le service de radiotherapie pour leur irradiation loco régionale Il n'y a donc pas d'inconvenient a etaler l'irradiation ovarienne On délivre 1 500 rad en 2 a 3 semaines au moyen de deux seances hebdomadaires

Dans le deuxieme cas, la castration est realisee seule, l étalement est alors ramene à moins d une semaine Le nombre des seances est de 3 chez les femmes proches ou contemporaines de la menopause et de 4 chez les femmes plus jeunes Une dose de 300 rad est delivrée a chaque séance, de telle sorte que la dose totale aux ovaires varie de 900 à 1 200 rad en 3 ou 5 jours Deux malades, qui avaient reçu des doses pour l une inferieure et pour l autre égale a 800 rad, ont du etre soumises a une irradiation complémentaire au bout de quelque mois

Sur le plan technique, il faut encore attirer l attention sur deux points Tout d'abord, il est prudent de s assurer par un examen gynécologique préalable qu aucune masse importante situee dans le petit bassin ne modifie la situation des ovaires De plus, il est absolument necessaire de verifier par des radiographies de controle, pratiqués avec le faisceau du rayonnement qui sert à traiter la malade, que le champ d irradiation couvre bien l ensemble du petit bassin, et donc le volume-cible tel que nous l avons défini Cette vérification est encore plus imperative chez les femmes obèses dont la peau est très mobile La plupart des échecs de la castration par l irradiation viennent certainement soit d'une balistique défectueuse, soit d une dose insuffisante L observation d'une certaine rigueur sur le plan technique met à coup sur à l abri de ces échecs La menopause peut etre obtenue par une irradiation simple, peu astreignante pour les malades, et toujours efficace, si quelques règles élémentaires sont respectées

l ovariectomie est pratiquee lorsque l etat de la malade oblige a rechercher une action immediate par exemple en cas de métastases osseuses ou lorsqu il existe des lesions gynecologiques associées

Il faut souligner un point important La technique d irradiation doit etre rigoureuse si l on veut eviter les echecs qui ont ete parfois rapportes et qui risquent de jeter injustement le discrédit sur la méthode, alors qu ils sont uniquement dus a une technique defectueuse

RESUMÉ

Afin de savoir quel est de la chirurgie ou des radiations le moyen physiologiquement le plus efficace et techniquement le plus commode pour réaliser la castration une comparaison des deux techniques a été réalisée Le test de comparaison choisi est le dosage des gonadotropines excrétées dans les urines deux et six mois apres la castration Sur la base de ce test un tres léger avantage serait à porter au crédit de la castration par les radiations Par ailleurs les deux techniques ont été comparées sur le plan clinique en fonction de leurs avantages respectifs et des risques qu elles font courir aux malades Aucun autre argument que la facilité d exé cution de l irradiation n a pu etre retenu en faveur de l une ou l autre méthode

SUMMARY

Surgery and radiotherapy have been compared with a view to determining which gave the more effective result and which was the more convenient in producing castration in cases of cancer of the breast Tests of the amount of gonadotropin contained in the urine two and six months following castration revealed a slight advantage in favour of radiotherapy The respective advantages of the two methods have al o been compared clinically with reference to the hazards involved Neither method exhibited any outstanding advantage apart from the ease with which irradiation could be applied

ZUSAMMENFASSUNG

D e Resultate bei der operativen Behandlung oder der Strahlentherapie wurden verglichen um zu bestimmen welche Methode die gunstigste und bequemste sei um Kastration be m Brustkrebs zu erzielen Es ergab sich bei quantitativer Gonadotropin Bestimmung im Urin zwei und sechs Monate nach der Kastration dass Strahlentherapie etwas gunstiger war D e respektiven Vorteile beider Methoden wurden auch klinisch im Verhaltnis zu den Risikos vergl chen Keine der Methoden wurde prinzipiell besser als die andere gefunden mit Ausnahme davon dass Strahlentherapie einfacher auszufuhren war

douloureux comme dans le cas des metastases osseuses Bien qu'aucune *indication valable n'existe* sur les mouvements du milieu hormonal dans les jours qui suivent immédiatement la castration par l'une et l autre méthode, et que des résultats spectaculaires aient été enregistres dans ces conditions par l'irradiation, il semble que l'on puissse encore accorder dans ces cas particuliers un prejugé favorable a l'ovariectomie dont l'action est plus brutale et plus precoce Nous faisons donc appel au *chirurgien* chaque fois que l'état de la malade fait rechercher un effet immédiat

Par ailleurs, il y a lieu aussi de considérer les malades qui présentent une affection gynécologique associée tumeur uterine ou ovarienne, annexite L'avis du gynécologue est alors toujours demande pour s assurer que ces lésions gynécologiques ne justifient pas par elles memes une intervention chirurgicale qui pourrait etre mise à profit pour pratiquer l ovariectomie bilatérale

En dehors de ces deux situations particulieres, nécessité d une action *immédiate,* affection gynécologique associee indiquant d'avoir recours au chirurgien, toutes les malades qui doivent etre castrées sont a l'I G R confiées au radiothérapeute

Conclusions

A l Institut Gustave Roussy, la castration complete le traitement du cancer du sein chez toutes les malades non menopausees, a l exception de celles qui, *parmi les malades opérables d emblée, presentent des ganglions non métastatiques*

Afin de savoir quel est, de la chirurgie ou des radiations, le moyen physiologiquement le plus efficace pour realiser la castration, une comparaison des deux techniques a éte realisee Le test de comparaison choisi était le dosage des gonadotropines excretees dans les urines deux et six mois apres la castration Sur la base de ce test, un tres léger avantage serait à porter au crédit de la castration par les radiations

Il semble donc que sur le plan de l efficacité, on peut sans inconvenient utiliser indifféremment l'ovariectomie ou l irradiation ovarienne, ainsi que l'indiquent par d'autres methodes les travaux de DICZFALUSY et de NISSEN-MEYER

Par ailleurs, les deux techniques ont été comparées sur le plan clinique en fonction de leurs avantages respectifs et des risques qu elles font courir aux malades Aucun autre argument que la facilité d exécution de l irradiation n'a pu etre retenu en faveur de l une ou l'autre méthode

A l Institut Gustave Roussy, c est donc la castration par les radiations qui a été en définitive préferée en raison de la simplicité de sa réalisation Cependant

Book reviews

STRAHLENSCHUTZ IN FORSCHUNG UND PRAXIS Band 5 Jahrbuch der Vereinigung deutscher Strahlenschutzarzte Herausgegeben von H J Melching W Erik H Keim und H A Ladner 238 Seiten 7 Abb 1 Farbtafel 28 Zeichnungen und 23 Tabellen Rombach Freiburg i Br 1965 Preis 49 DM

The book contains a number of lectures given at a course organized in 1964 by the German Association of Radiation Protection Physicians The first four papers concern recent progress in radiation genetics of fruitflies mice and men and the possibility of influencing the genetic effects of radiation by chemical agents They serve well to illustrate the complicated condi tions in this field the difficulties of utilizing animal experimental data for judging the effects in human subjects and the uncertainty with which all quantitative assessments of hazards to man are beset

Pretty much the same can be said about the papers that follow on radiation induced mal formations especially in mice irradiated in utero Not only the gross anatomical but also microscopic submicroscopic and biochemical effects are considered and it is stressed that somet mes it is impossible to demonstrate a causal relationship between a malformation and previous irradiation The multitude of other agents producing similar effects are mentioned

A third group of papers concern the financial responsibility for radiation injury and questions of insurance ranging from minor injuries to personnel and patients in medical work to reactor catastrophes involving claims for hundreds of million dollars National legisla tion and international conventions (especially in the German Federal Republic and Euratom) are discussed

The last series of papers under the heading The radiation risk attempt to define the con cept risk to express the radiation risks quantitatively and to compare them with other profess onal hazards The measures necessary for reducing the dangers are contained in two papers discussed in rather legal terms Another paper is concerned with dangers due to cl nicians with inadequate special training who carry out fluoroscopy for too long and at too high dose rate Finally the risk from contaminated foodstuffs under present conditions is discussed and found to be low Measures to be taken in case of heavier contamination should be decided by balancing radiation risks against those arising from such countermeasures as evacuation and diet changes

The present reviewer is not qualified to pass a fair judgment on the legal parts of the book but the other sections have been found valuable and interesting Recent scientific data and the viewpoints given should be helpful in forming a more balanced view than is generally encountered on radiation dangers

Sten Benner

PROGRESS IN EXPERIMENTAL TUMOR RESEARCH Vol 7 Edited by F Homburger 351 pages 42 figures and 25 tables S Karger A/G Basel 1965 Price 95 SFR

The present Volume 7 of this series contains seven chapters covering a variety of important aspects on neoplasia

The control mechanisms in the normal and neoplastic cell is the subject of a chapter by H C Pitot and Y S Cho the experimental basis for th s discussion being mainly the liver hepatoma system The authors put forward three different possible mechanisms for the neo-

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TREATMENT OF MALIGNANT TUMOURS OF PARANASAL SINUSES

by

LARS R HOLSTI and REIJO RINNE

The majority of the carcinomas of the paranasal sinuses originate in the mucosa The growths are difficult to treat as they spread easily to the surround ing vital organs via the base of the skull or the orbit Radiotherapy has a prom inent role in the treatment especially when combined with operation and its evolution in recent years has indisputably improved the facilities for managing these conditions

The material of our clinic has been reviewed only once previously in the literature (MUSTAKALLIO & HAMALAINEN 1946) The aim of the present in vestigation was to analyse the therapeutic results achieved by surgical and radiologic treatment as well as by the latter alone All the follow up examina tions were performed at the clinic

Material This consisted of 289 patients registered in the period 1950—1962 The frontal sinuses were involved in only six of the patients The neoplasm was in most of the patients situated in the maxillary antrum or the ethmoids these sites are therefore considered together There were 167 males and 122 females which gives a sex ratio of about 3 2 A more or less clear preponder

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Submitted for publication 30 September 1966

plastic transformation One is that cancer is a genetic disease which would include qualitative and quantitative changes in the genetic information of the cell The authors do not feel that this possibility is very likely since every one of the hepatomas although exhibiting a variety of genetic defects when compared to normal cells appears to have a unique phenotype the only common denominator being uncontrolled growth Another possibility is based on the regulatory scheme advanced by Jacob & Monod and would mean that environmental stimuli (carcinogens) might bring about a *permanent* cellular change (*neoplasia*) by altering established regulatory circuits As a third mechanism favoured by the authors the possible importance of an increased stability of messenger RNA (constituting stable templates for the enzymes of DNA synthesis) as a primary lesion in the neoplastic cell is emphasized

The chapter by G I Abelev contains an extensive review of the antigenic structure of normal liver and hepatomas It is concluded that the differentiated liver parenchymal cells constitute a mosaic of discrete relatively independent organo-specific antigenic components During carcinogenesis individual components of this pattern may disappear while others are completely preserved which is in accordance with Foulds s concept of tumor progression The production of fetal alpha globulin by a number of hepatomas and the finding of this protein also in the serum of patients with hepatocellular tumours is discussed and its possible diagnostic *importance is pointed out*

The characteristics of the variants of Rous sarcoma virus which are pathogenic for mammals are reviewed in great detail by L A Zilber The interaction in vivo and in vitro between these viruses and cells of rats mice rabbits Syrian and Chinese hamsters guinea pigs monkeys calves and human subjects is described The maintenance of the viral genome in the induced tumors and the existence of common tumor specific antigens is considered

In a chapter by P G Stansly the non oncogenic infectious agents often found to be associated with experimental tumors are discussed It is emphasized that the tendency of e g viruses to accumulate in passages and even primary neoplasms must be kept in mind when looking for the possible viral etiology of tumors It is pointed out that contaminating agents may also provide a significant contribution to the apparent disease picture in neoplastic hosts

Basic features of radiation carcinogenesis are summarized by G W Casarett Consideration is given to the important factors of both the direct mechanism when the irradiation acts directly on the genetic material of the cells of origin and of the indirect mechanism going through alterations of the environmental components (hormonal or metabolic imbalances or viral activation)

The chromosome changes demonstrable in primary neoplasms are critically evaluated in a chapter by P C Nowell Finally L L Bennett has reviewed the modes of action of the antileukemic phthalanilides comparing them with related but inactive substances

This volume of the series offers several useful separate reviews of a variety of different fields of cancer research The broad scope of the volume appears to have been deliberately chosen in an attempt to ensure that the series covers all important aspects of cancer research

Hans O Sjögren

Histology The diagnosis was generally confirmed by biopsy prior to therapy, only ten patients were not verified histologically All the patients (137) with evidence of epidermoid carcinoma were classified as squamous cell carcinoma except when anaplasia complicated the classification These pa tients were included in the group of anaplastic carcinomas (84) together with the scirrhous solid and papillomatous carcinomas Adenomatous carcinomas were infrequent and present only in 14 patients (4 8 %) Malignant tumour was the diagnosis in 18 patients, and there were 21 different sarcomas The mixed group 5 patients included one with a glioma another with a malignant chordoma and a third with a malignant teratoma

Treatment The commonest method of treatment was surgery followed three to four weeks later by radiotherapy The operation was radical whenever possible and the involved tissue was removed or cauterized right down to healthy tissue Both oral and facial approaches were used and the os maxillare was often extirpated The regional lymph nodes were also removed if possible The material included 6 patients in whom the treatment consisted of operation alone postoperative treatment was administered mostly as external therapy Roentgen irradiation was the commonest mode of treatment (factors 190 to 250 kV and HVL 1 0 to 1 6 mm Cu) Teleradium therapy was given post operatively to 39 patients (FSD 6 cm, radium source 5 g Ra equivalent)

Postoperative treatment was applied for 33 patients with the 400 Ci tele cobalt unit that has been available since the autumn of 1956 The dose in roentgen therapy was mostly 5 000 R over 4 to 5 weeks (range 4 500 to 5 550 R) calculated from depth dose tables The dose was roughly the same with the teleradium method as with telecobalt therapy and was mostly 6 000 R (range 5 000 to 7 000 R) The treatment time however was much shorter in tele radium therapy i e 2 to 3 weeks compared with 5 to 6 weeks in cobalt tele therapy Cobalt peas were applied intracavitarily in 29 patients Radiation therapy alone was administered to 49 patients and the tumour dose was 5 000 to 6 000 R in roentgen therapy and over 6 000 R in teleradium and cobalt therapy

Three sometimes four fields were used The shortage of staff in telecobalt therapy precluded an individual treatment plan for every patient and the treatment was based on model plans or depth dose tables Since the autumn of 1962 however every scheme has been prepared individually Examples of the dose distribution in roentgen teleradium and telecobalt therapy as well as field planning are given in Fig 2 With a few exceptions the orbit was not included in the treatment area The ethmoid sinuses if involved were generally treated through an additional narrow field placed between the eyes However

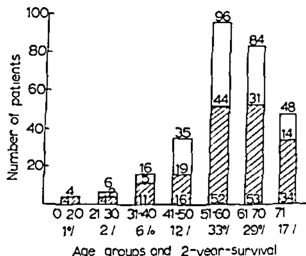


Fig 1 Age distribution of the material in per cent and 2 year survivals in different age groups The blank areas in the columns indicate the number of patients surviving more than two years

ance of males has also been reported by earlier writers (DALLEY 1959) The age distribution is given in Fig 1, from which may be seen that most of the patients (79 %) were over 50 years old This agrees more or less with the report of LARSSON & MÅRTENSON (1954) although the 41—50 age group was smaller in the present series than in the Swedish material The prognosis by age groups is given in Fig 1, which will be discussed later The follow up period covered a minimum of two years

Clinical classification It is difficult to find a classification reliable for every patient ÖHNGREN (1933) classified his patients by dividing the antrum into four groups The anatomy of the maxilla was employed by DALLEY (1959) as the basis for his distribution, i e frontal, alveolar, zygomatic and palatine groups The present material was divided according to spread as follows

1 The lesion was limited to one maxillary antrum, no (roentgenologic) bone destruction was evident

2 The lesion was unilateral or penetrated slightly into the ethmoids with bone destruction or extension to the orbit or oral cavity Prognostic considerations for this group led to three subgroups (A) the lesion was limited to one maxillary sinus, with or without the ethmoid, (B) the lesion invaded the orbit, and (C) the lesion extended to the mouth, this latter is a serious complication, for the outcome depends on the lymphatic drainage

3 The growth extended to the pterygopalatine fossa, to the base of the skull with or without cranial nerve involvement, was bilateral or very large, or extended to both the orbit and the oral cavity

4 Regional lymph node meastases were present

5 Distant metastases were present

Survival was calculated from the start of therapy No patients have been ex cluded from the material

Clinical symptoms These depend on the spread of the tumour in the paranasal sinuses The commonest complaints are pain in the cheek and chronic nasal disorders (MUSTAKALLIO & HAMALAINEN 1946 LARSSON & MARTENSON 1954 CANTRIL et coll 1962) These were also the commonest symptoms in the present material and occurred in over half of the series A purulent nasal discharge and nasal congestion are typical symptoms of common sinusitis although if unilateral the possibility of malignancy must always be remem bered especially when the patient is of advanced age More specific signs of tumour such as swelling of the cheek or face epistaxis displacement of the eye and visual disturbances as well as symptoms from the palate and toothache do not arise early but may be fairly common reasons for the patient seeking advice

A visible tumour bulge appeared in the oral cavity of 75 patients in the present series In 38 of these the mass was confined to the maxillary sinus and oral cavity and in the others it extended to the nasopharynx base of the skull or the orbit Fifteen patients had cervical lymph node metastases

Fifty patients complained of disturbed vision surgery revealing that the orbit was involved in 25 of these A considerable proportion of the patients were thus in an advanced state of disease There has consequently been no change in the situation from the 1930 s and 1940 s when the symptoms were practically the same in the material reviewed by MUSTAKALLIO & HAMALAINEN (1946)

A roentgenologic diagnosis of the condition is possible only if bone destruc tion is present All the patients of the present series were examined roentgeno logically Many were examined tomographically and more recently pantomo graphy (PAATERO 1960) was included in certain instances

Results

The survival rates in the different age groups may be seen in Fig 1 The blank areas in the columns represent the patients who survived for over 2 years The prognosis was markedly better in the 41—70 year age group than for the younger patients 219 patients were followed for 5 years The 2 and 5 year crude survival rates of 40 % and 28 5 % respectively are given in Fig 3 Out of 117 patients seventeen or 15 % survived for 10 years

The results according to clinical spread appear in Table 1 Extension of the growth to the skull base orbit or oral cavity definitely impairs the prognosis

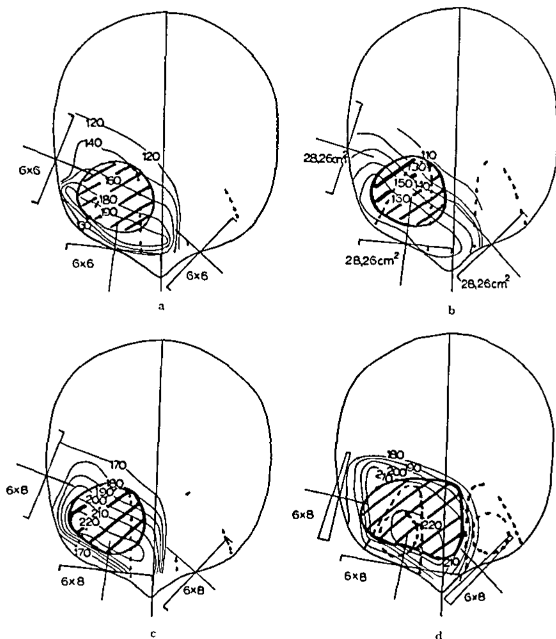


Fig. 2. Dose distribution with different types of radiotherapy: 250 kV roentgen (a), teleradium (b), 400 Ci cobalt (c), and 3 000 Ci cobalt with wedge filters (d).

when the eyes must be protected, it is difficult to achieve an effective tumour dosage in this way. In recent years the orbit has been evacuated primarily in 16 patients, in whom it was involved, and this has considerably facilitated planning and treatment. Treatment was administered six times a week

Survival was calculated from the start of therapy No patients have been excluded from the material

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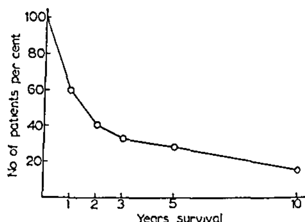


Fig. 3. Crude survival rates for the material.

Infiltration into the nasopharynx or the bones of the base of the skull is the most unfavourable prognostic sign (5 year survival 19 %). Regional lymph node involvement makes the prognosis poor. The 5 year survival rate was 52 % for conditions confined to the antrum and 13 % when the bones of the maxillary sinus were infiltrated or there was spread to the ethmoids. The mean survival time of the patients who died was also a clear indication of the decline in the prognosis with the spread of the process.

Twenty three patients died of intercurrent conditions, such as suicide, intestinal obstruction, and heart disease. In 18, there was no recurrence at death, none was lost to follow up. The corrected 5 year survival rate was thus 62/201, i. e. 31 %.

The 2- and 5 year survivals, according to the histologic classification, are given in Table 2. The 5 year survival rate was 23 % for epidermoid and 36 % for anaplastic carcinomas. The adenocarcinoma group is small but the survival rate for this group was distinctly higher than for the other groups. LARSSON & MÅRTENSSON (1954) noted that adenocarcinomas are generally local and do not produce metastases; the prognosis in their material was however poor. The prognosis for sarcomas and unclassified malignant tumours is of the same order as that for squamous cell carcinomas.

The prognosis for the ten patients without histologic verification was worse than for the other groups (Table 2). All the growths appeared clinically as malignant tumours, four of the patients had distant metastases and six locally advanced disease. Five of them received no treatment because of bad general condition, four received radiotherapy alone (1 000 to 6 000 R) and one was primarily treated elsewhere. Only three patients lived longer than one year, and one patient longer than two years (2 years 9 months).

The correlation between the results and the type of therapy is apparent from

Table 1

Number of patients and 2 year and 5-year survivals in relation to spread of tumour

Clinical spread	Number of patients	Survival 2 years	Survival 5 years	Mean survival time until death months
1 Local unilateral no bone destruction	29	18 (62)	13/ 25 (52)	40 8
2 A Bone destruction or ethmoids involved	63	35 (56)	21/ 49 (43)	28 9
2 B Orbital cavity involved	53	25 (48)	13/ 40 (33)	15 3
2 C Extension to oral cavity	38	17 (45)	7/ 32 (22)	18 0
3 Skull base or nasopharynx involved bilateral	55	16 (29)	6/ 32 (19)	14 6
4 Regional lymph nodes infiltrated	43	4 (9)	2/ 34 (6)	8 8
5 Generalised metastases	8	0	0/ 7	7 0
Total	289	115 (40)	62/219 (28 5)	

Table 3 The combined therapy group operation and postoperative radiotherapy was the largest one with 200 patients Conventional roentgen therapy was given to 99 patients teleradium to 39 and telecobalt to 33 patients Surgery was generally *radical* The 5 year results were exactly the same in the groups that received conventional roentgen radiation and teleradium postoperatively The 2 year results of telecobalt therapy were better than both these although the number of patients followed for 5 years is still so small that a definite evaluation is not possible Four out of 14 patients survived for 5 years Local isotope therapy postoperatively was not convincing in this material but only six patients were treated in this way On the other hand surgery and local isotope therapy with cobalt pearls and external roentgen therapy gave the best results and 40 % of the patients survived for 5 years The number is again small In many of the patients the cobalt peas were introduced into the maxillary sinus in connection with surgery Additional external radiotherapy was generally administered in the form of roentgen irradiation or sometimes teleradium therapy the dose was 3 000 to 4 000 R

Radiotherapy alone was given to 49 patients but the results were distinctly

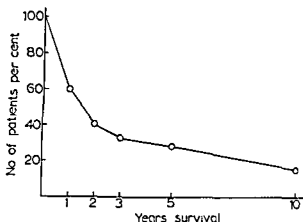


Fig 3 Crude survival rates for the material

Infiltration into the nasopharynx or the bones of the base of the skull is the most unfavourable prognostic sign (5 year survival 19 %) Regional lymph node involvement makes the prognosis poor The 5 year survival rate was 52 % for conditions confined to the antrum and 13 % when the bones of the maxillary sinus were infiltrated or there was spread to the ethmoids The mean survival time of the patients who died was also a clear indication of the decline in the prognosis with the spread of the process

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The prognosis for the ten patients without histologic verification was worse than for the other groups (Table 2) All the growths appeared clinically as malignant tumours, four of the patients had distant metastases and six locally advanced disease Five of them received no treatment because of bad general condition, four received radiotherapy alone (4 000 to 6 000 R) and one was primarily treated elsewhere Only three patients lived longer than one year, and one patient longer than two years (2 years 9 months)

The correlation between the results and the type of therapy is apparent from

Table 3

Number of patients and survival times in relation to method of treatment

Treatment	Number of patients	Survival 2 years	5 years
Radiotherapy alone	49	15 (30)	5/ 34 (15)
Conventional roentgen	32	9 (28)	4/ 24 (17)
Teleradium	11	4 (36)	1/ 8 (12 5)
Telecobalt	6	2 (33)	0/ 2
Surgery + radiotherapy	200	81 (40 5)	54/159 (33 5)
Surgery + roentgen	99	46 (46 5)	29/ 80 (36)
Surgery + teleradium	39	15 (38 5)	12/ 33 (36 5)
Surgery + telecobalt	33	17 (51 5)	4/ 14 (28 5)
Surgery + Co pearls	6	2 (33)	1 6
Surgery + Co pearls + roentgen	23	12 (52)	8/ 20 (40)
Surgery alone	6	2 (33)	1/ 5
No treatment	19	1 (5)	0/ 14
Treated elsewhere (usually surgery + *roentgen*)	14	5 (36)	2/ 10 (20)
Total	289	115 (40)	62/219 (28 5)

Recurrences The recurrences were usually at the site of primary tumour i e in the antrum They also often arose at the border of the treatment mass where the radiation dose was obviously not sufficient e g in the ethmoids the orbit or retro orbitally The rate at which recurrences appeared can be correlated with the clinical degree of spread the more far reaching the process the more rapid the appearance of recurrence and the poorer the prognosis It is sometimes difficult to draw a line between a malignant remnant and recurrence The present authors have considered as a residue such malignant tissue as was left 6 months after treatment Any growth that was detected 6 months or later after the treatment the therapeutic area having in the interval been macroscopically free of tumour was regarded as a recurrence There is a clear prognostic difference between the two groups

One hundred and seventy nine patients with recurrent and residual tumours followed for a minimum of 2 years after repeat therapy were analysed to evaluate the prognosis in the above groups Twenty five patients primarily treated elsewhere and those who were primarily in an advanced stage of the disease were excluded Then 154 patients remained 65 of whom received no repeat therapy or were given inadequate radiotherapy (less than 3 000 R)

Table 2

Survival times in relation to different types of tumour

	Number of patients	Percentages	Survival 2 years	Survival 5 years
Squamous cell carcinoma	137	47.4	46 (34 %)	23/99 (23 %)
Anaplastic carcinoma	84	29.0	40 (48 %)	24/67 (36 %)
Adenomatous carcinoma	14	4.8	10 (71 %)	7/11 (64 %)
Unclassified malignant tumour	18	6.2	8 (44 %)	4/16 (25 %)
Sarcoma	21	7.4	8 (38 %)	3/12 (25 %)
Other lesions	5	1.7	3 (60 %)	1/2
No histology	10	3.5	1 (10 %)	
Total	289	100.0		

inferior to those of the combined therapy. The prognosis of patients of this group was however poorer from the outset: surgery was not performed because of the wide spread of the tumour or the patient's poor general condition.

The material included only six patients who were subjected to operation alone; one survived for 5 years (Table 3). None of the patients given no treatment at all, on account of a poor general condition, survived for 5 years, but 5 % lived for 2 years.

Viewing the material as a whole, the therapeutic method had not been entirely uniform, and for this reason the authors selected the operable cases that had been treated according to a uniform therapeutic principle. Radical surgery, followed by radiotherapy with at least 4 000 R, was the treatment for this selected series of 112 patients. The 2-year survival rate was 55 % and the 5-year rate 40 %. This selected material included 45 patients in whom the growth was local or infiltrated the wall of the maxillary antrum but did not perforate it (Table 4). The 2-year survival rate was 73 % and the 5-year rate 55 %. This indicates clearly the great influence on the prognosis of an early diagnosis.

Orbital evisceration was performed primarily in only 16 patients, but orbital involvement was established considerably more often. Ten of these patients had a process that extended to the base of the skull or to the oral cavity, in consequence of which the results were not good. Six of these 16 patients lived for over 2 years, and one out of two lived for 5 years.

Six patients lost the sight of the eye on the side of the tumour as a therapeutic complication, although the eye was always protected with lead during treatment.

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Su gery lone	6	2 (33)	1/ 5
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Table 4

Number of patients and survival times in a selected material treated with radical surgery and radical radiotherapy in relation to the spread of lesions

Clinical spread	Number of patients	Survival	
		2 years	5 years
Local or antral wall involved	45	33 (73 %)	25 (55 %)
Perforation to orbital or oral cavity	67	27 (40 %)	20 (30 %)
Total	112	63 (56 %)	45 (40 %)

owing to their poor general condition. Only three of these untreated recurrences survived for more than two years.

Tables 5 and 6 reveal the effect of treatment on 44 residual tumours and 45 recurrences. This consisted either of radiotherapy alone, 3 000 to 6 000 R (mostly 3 000 to 4 000 R) or combined operation and radiotherapy. Of the patients with recurrence, 38 % survived for over two years, whereas only 13 % of those with a residue lived for two years after repeat therapy. The treatment was essentially the same in both groups. The difference in the results may be due to the smaller radiosensitivity of residual tumours because of their poorer vascularity and oxygen supply. The condition of the tumour bed obviously plays an important role. Combined therapy seems to yield slightly better results than radiotherapy alone.

It appeared that the skin of several patients would not tolerate a new course of external therapy. In these patients, the cobalt pears were inserted into the operation cavity after further surgery or were applied without operation through the persistent drainage hole. The eye was enucleated in connection with the treatment of the recurrence in 17 patients. Energetic management of recurrence is rewarding, many patients derived long lasting benefit from it and in some no further recidives had appeared after a follow up period of two years.

Discussion

There is no generally accepted clinical classification of tumours of the maxillary antrum. SISSON et coll. (1963) presented a classification based on the TNM system. This, however, requires antral exploration and was thus not serviceable in the present retrospective materials. The present authors grouped their material according to the roentgenologic findings and spread established at operation. Only 29 out of 289 patients had no bone destruction or spread beyond

Table 5

Treatment of residual tumours — Primary treatment was combined surgery and radiotherapy in 36 patients and radiotherapy alone in 8 patients

Treatment	Number of patients	Survival	
		1 year	2 years
Surgery + radiotherapy	20	8	4
Radiotherapy alone	24	7	2
Total	44	15 (34)	6 (14)

Table 6

Treatment of recurrences — Primary treatment was combined surgery and radiotherapy in 36 patients and radiotherapy alone in 9 patients

Treatment	Number of patients	Survival	
		1 year	2 years
Surgery + radiotherapy	21	15	10
Radiotherapy alone	24	13	7
Total	45	28 (6?)	17 (38)

the maxillary antrum WILLE (1947) reported that 203 of 209 patients presented roentgenographic evidence of bone destruction on admission Roentgenologic changes were also used by BACLESSE et coll (1960) as the basis of classification

Histologic classification inevitably results in small sub groups However surprisingly small differences were encountered in the therapeutic results between the different groups in the present material The results seemed to be best in the adenocarcinoma group which was however very small The prognosis was poor in cases with lymph node involvement DALLEY s (1959) material had less deterioration from glandular involvement Lymph glands should be removed operatively The therapeutic results were better with combined operative therapy and radiotherapy than with radiotherapy alone the patients managed with radiotherapy alone were inoperable The therapeutic results in the present series were comparable with those achieved elsewhere (Table 7)

Electrosurgery intracavitary radium application and external roentgen therapy were the therapeutic methods of choice in the 1930 s and 1940 s MUSTAKALLIO & HAMALAINEN 1946 TOD 1948 DEVINE & SCANLON 1957)

Table 7

Comparison between survivals in certain series

Authors and treatment period	Number of patients	5 year crude survival percentage	Treatment
LARSSON & MÅRTENSON 1940—1947	294	23	All methods
GIBB 1940—1950	334	18	All methods
SNELLING 1936—1950	115	28	Roentgen + surgery
DALLEY 1933—1955	87	30	All methods
BACLESSE et coll 1929—1953	94	20	Roentgen alone
Present series 1950—1959	219	28 5	All methods

Intracavitary application of radioactive isotopes has also been tried (JAMES 1957) External megavoltage therapy has gained more ground recently, and preoperative radiotherapy, used earlier by e g LARSSON & MARTENSON (1954), has won even more widespread acceptance (SPRATT et coll 1964, MOSS 1965) Radiotherapy has been applied postoperatively at our clinic *until the last few years but is now being replaced by preoperative radiotherapy* after a Luc Caldwell incision External cobalt teletherapy is now the sole method of radiotherapy for maxillary antrum carcinoma

Cobalt teletherapy gives an adequate dose distribution especially when wedge filters are used (Fig 2) On the other hand, electron therapy is not beneficial because anatomic conditions make the dose distribution uneven Cavities increase the irregularity for the same treatment volume more than the presence of bone and other tissue

Conventional roentgen therapy with 4 500 to 5 000 R in 5 to 6 weeks has been regarded as sufficient (DALLEY 1959) SPRATT et coll used 6 000 R over 6 weeks A skin dose of 3 000 R to three or four fields over a period of 30 to 40 days was regarded as a full dose in the present material The authors dose nowadays for cobalt teletherapy is 6 000 rad minimum over 6 weeks or, for split course therapy, over 8 weeks FRIEDMAN (1959), in his study of tumour reaction and epithelitis with supervoltage (2 MeV) came to the conclusion that the tumour dose should be considerably higher, even 30 % to 50 % greater with 2 MeV *than with orthovoltage He even recommended doses* of 9 000 rad

Primary therapy generally has to be sufficiently intensive for the treatment of residual tumours, and for recurrences it is seldom as successful as for the primary growth Residual malignant tissue and recurrences grow in scar tissues with deficient circulation and poor oxygen *supply in which it* is difficult to destroy the neoplasm by radiotherapy The dose should be at least as high as

in primary therapy preferably higher and this is not always possible even with megavoltage therapy The treatment of recurrences is rewarding but their prevention is even more important

The authors are of the opinion that the spread of the growth to the floor of the orbit calls for radical therapeutic measures Permanent results are otherwise impossible to achieve and recurrences appear regularly Adequate irradiation without damage to the eye is almost impossible in practice The later development of cataract in roentgen therapy cannot be totally prevented by lead shields (DALLEY 1959) The authors noted that recurrences occurred mostly in the orbital fundus after conservative radiotherapy The correct method when the ethmoids or the floor of the orbit are involved is as pointed out by MACCOMB & FLETCHER (1957) exenteration of the orbit It is otherwise impossible to achieve an adequate radiation dose to the tumour area

Acknowledgements

The histologic examinations were performed by Prof E Saxen (1950—1960) and Docent P Holsti (since 1960)

SUMMARY

The material comprised 289 patients with histologically verified carcinoma of the paranasal sinuses mostly treated by surgery and postoperative radiotherapy The 2 year crude survival rate for the total material was 40 per cent and the 5 year rate 28 5 per cent

ZUSAMMENFASSUNG

Ein Material von 289 histologisch verifizierten Fallen von Krebs der Nasennebenhohlen wurde chirurgisch und mit nachfolgender Bestrahlung behandelt Nach zwei Jahren waren 40 Prozent von den Patienten am Leben und nach funf Jahren 28 5 Procent

RÉSUMÉ

Les auteurs présentent 289 cas de cancer des sinus de la face vérifié histologiquement traités pour la plupart par chirurgie et radiothérapie post opératoire Le taux brut de survie a deux ans pour l ensemble a été de 40 pour cent et le taux a cinq ans de 28 5 pour cent

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TREATMENT OF ISOLATED LUNG METASTASES

by

JO ASVALL AXEL SANDERUD and LORENTZ NITTER

The appearance of pulmonary metastases in malignant disease is usually an indication that treatment can only be palliative These metastases usually represent a haematogenic spread of the tumour cells and suggest that general dissemination is occurring

However the literature now contains encouraging reports on the surgical treatment of lung metastases in more than 600 patients It is the aim of this article to review some of the more recent publications on the subject and to present a material of 20 additional patients This has been done in order to evaluate possible prognostic factors and determine whether irradiation can offer an alternative method of treatment

ALEXANDER & HAIGHT (1947) made the first comprehensive study of the problem by collecting a total of 24 patients operated upon for solitary pulmonary metastases Since then numerous reports have been published. WILKINS et coll (1961) managed to collect a total of 355 patients from the literature and added 67 patients of their own in an article that contained an extensive review of the literature (to which the interested reader is referred)

By far the most important single group of patients was presented by MOERSCH & CLAGETT in 1961 (165 patients) to which THOMFORD et coll (1965) added 40 more MERLIER et coll (1963) and POLK et coll (1965) added a further 37 patients to the list making a total of 664 patients up to the end of 1965

Some interesting conclusions may be made from these reports

Submitted for publication 2 November 1966

Table 1

Three and five year survival figures from previously published materials on the surgical treatment of lung metastases

Author	Number of patients	Survival rate	
		3 years	5 years
Alexander & Haight (1947)	24	51 %	—
Gliedman et coll (1957)	29	40 %	22 %
Ehrenhaft et coll (1958)	37	21 %	—
Wilkins et coll (1961)			
Literature survey	355	40 %	37 %
Present material	67	38 %	26 %
Thomford et coll (1965)	205	39 %	30 %
Polk et coll (1965)	17	39 %	—

Survival rate The survival rate after surgical removal of a lung deposit seems to be fairly good Most of the more important studies reveal a 3 year survival figure of about 40 % (Table 1) and a 5 year figure of from 22 % to 37 % The 7 year survival in the survey of THOMFORD et coll was found to be 23 %

Prognosis and the primary/secondary tumour interval It is often thought that a long interval between treatment of the primary growth and the appearance of lung metastases is of great importance to the ultimate success in the treatment of the latter (ALEXANDER & HAIGHT) Some controversy regarding this problem does exist, however GLIEDMAN et coll (1957) could find no correlation between the length of the interval and the prognosis WILKINS et coll reported a better 5 year *survival among patients who developed metastases more than 5 years* after the primary than among those in whom metastases appeared earlier MOERSCH & CLAGETT suggested the crucial time limit to be one year after treatment of the secondary deposits This was later confirmed by the more extensive material of THOMFORD et coll the 3 year survival figure for patients with metastases less than one year after the primary tumour was 22 % compared to 42 % and 40 % for those with metastases at respectively 1 to 4 years or more, later

Type of tumour and prognosis Carcinomas have a somewhat better prognosis than sarcomas (MOERSCH & CLAGETT) those originating in the kidney large bowel and uterus may have the best prognosis and melanomas the worst (WIL-

Table 2

Results and data of treatment for the 13 patients in the group operated upon

Ca No	Type of primary tumour	Operation	Observation time	
			Months	End result
1	Ca test s (embryonal)	*Lobectomy*	*101*	*No recurrence*
2	» (terato d)	Segmental res	128	No recurrence
3	Ca corp uteri (adenocarcinoma)	Pneumonectomy	40	Dead
4	» »	Segmental res	35	Recurrence
5	» »	Lobectomy	47	Dead
6	C renis (hypernephroma)	Lobectomy	86	No recurrence
7	» »	Local excis on	14	Dead
8	» (low diff carcinoma)	Segmental res	4	Dead
9	M l gnant melanoma	Segmental res	7	Dead
10	»	Segmental res	8	Dead
11	Ca ov ri (cystad fib)	Segmental res	23	No recurrence
12	Bone sarc (osteogenic)	Local excis on	5	Dead
13	Ca subl ng (quamous)	Local excision	10	No recurrence

KINS et coll) Apart from this it seems difficult to find good correlation between survival and the histologic type of the tumour

Particular types of tumours may produce surprising results Of the 23 patients with os eogenic sarcomas collected from the literature by WILKINS *et coll* six were known to be 5 year survivors a high figure considering the usually bad prognosis for this type of growth

B aring in mind that lung metastases usually indicate a haematogenous spread of malignant tissue the relatively good prognosis is somewhat difficult to under s and However the presence of malignant cells in the blood does not seem to prevent long term survival (ENGEL 1959) Experimental data have demonstrated that implantations of tumour fragments or tumour cell suspensions (even autologous ones in cancer patients) have a low frequency of take (GRACE & KONDO 1958)

Many emboli of tumour cells to the smaller vess ls in the lung parenchyma may be inactivated by a surrounding layer of hyaline thrombi finally replacing the cancer cells altogether as suggested by SAPHIR (1947) and others

Numerous unknown factors still cloud our understanding of what hinders or promotes the growth of blood borne metastases at the site where they finally lodge There seems to be no doubt however that viable metastases are often confined to the lung even at a late stage of generalized spread (FARREL 1935)

Table 3

Results and data of treatment for the 7 patients in the irradiated group

Case No	Type of primary tumour	Tumour dose rad/days	Observation time	
			Months	End result
14	Ca testis (embryonal)	5 400/23	52	No recurrence
15	» »	4 800/19	11	Dead
16	» »	1 900/11	17	Dead
17	» »	1 000/ 7	171	No recurrence
18	» (teratoid)	4 200/23	9	Dead
19	Malignant melanoma	4 700/40	26	No recurrence
20	Ca mammae	3 500/26	10	Dead

Material and Methods

Material. This consisted of patients treated between 1932 and 1965 who fulfilled the following requirements: (1) the primary tumour had been adequately treated, and there had been no local recurrences or other metastases until treatment of the lung deposits was initiated, (2) clinical and roentgen investigations indicated that the pulmonary metastases were solitary when the decision to treat was taken.

Two of the patients received part of their treatment at Department III of Oslo City Hospital (Ullevål).

The material includes a total of 20 patients, the youngest being 16 and the oldest 69 years of age. Sixteen of the tumours were carcinomas and four were sarcomas. The histologic types are given in Tables 2 and 3.

Symptoms and signs. Only seven of the 20 patients had symptoms that revealed the pulmonary metastases. Routine surveys made during a State Anti-tuberculosis Campaign revealed the condition in four, while the remaining nine patients were detected at follow-up controls. Nine patients had no symptoms whatsoever. Among the others, pain was the most frequent complaint, followed by cough and dyspnoea.

An increased sedimentation rate (i.e. more than 12 mm/hour) was present in seven patients at the time when the treatment of the lung deposit was initiated.

The clinical chest examination was of no value in the diagnosis.

Roentgen examination. The roentgen examination in every instance indicated that only one metastasis was present, and hilar node enlargement was never found.

Diagnosis This diagnosis was confirmed by histologic examination of the lung specimen in every one of the thirteen patients in the group treated by surgery and was based upon an evaluation of the roentgen appearances and the absence of any but the original primary growth in the irradiated group

Surgical treatment Thirteen of the patients were treated by surgery (Table 2) the operations included one pneumonectomy 3 lobectomies and 9 segmental resections and smaller excisions None of the patients had preoperative irradiation Only one patient (Case 1) was treated by postoperative irradiation (3 700 rad/26 days with 31 MeV gamma rays) to the mediastinum for good measure no involvement of the hilar nodes had been evident at the operation No hospital deaths occurred Postoperative complications were few (one cardiac infarction and one bronchial fistula) and responded well to treatment

Radiation treatment Seven patients were treated by irradiation of the lung metastases (Table 3) The treatment fields were limited to the tumour and a reasonably safe surrounding area The hilar lymph nodes were not included The tumour dose was calculated in rad This dose and the duration of treatment are given in Table 3 There was a substantial difference in the dose administered to the two patients (Cases 16 and 17) treated by conventional 175 kV roentgen therapy as compared with the other five patients who received treatment with 18 to 31 MeV gamma radiation from betatrons None of the patients experienced any noticeable side effects due to the irradiation

Results

As just mentioned the results for the two groups of patients are recorded in Tables 2 and 3 The observation time indicates the interval between the termination of treatment of pulmonary metastases and death, or for patients still alive until the most recent observation date

Eleven of the 20 patients died from recurrence of the neoplasm seven of them within the first year One patient (Case 4) had a recurrence but is still alive 35 months after treatment of the pulmonary deposit Eight patients are alive and without recurrences four of these have survived more than 5 years (7 years 2 months 8 years 5 months 10 years 8 months and 14 years 3 months respectively)

The crude survival rate for the whole group is 53 % after 3 years and 38 % after 5 years

Surgical treatment Both the patients with a growth of the testis are alive and without recurrence more than 8 and 10 years respectively after removal of the pulmonary metastases (Table 2)



a b

Pulmonary metastases before (a) and after (b) irradiation Persistence of infiltration 14 years after treatment

In only one patient was more than one cancer nodule found at the histologic examination of the specimen, this patient (Case 6) was alive more than 7 years after the operation which revealed two malignant hilar lymph nodes in addition to hypernephroma metastases in the pulmonary parenchyma

The two remaining patients with renal carcinoma as well as both the patients with a malignant melanoma and one with a bone sarcoma died comparatively soon after the operation they obviously failed to benefit from the treatment

Good palliation was obtained in the three patients with carcinoma of the corpus uteri, they all had quite long periods (25, 32 and 36 months, respectively) of freedom from symptoms before further metastases occurred

As regards the patient with a sublingual carcinoma the observation time is still too short (10 months) to permit an evaluation as to the value of the treatment

Radiation treatment As Table 3 indicates two of the five patients with carcinoma of the testis are alive and without recurrence more than 4 and 14 years, respectively, after treatment The remarkable radiosensitivity of one patient (Case 17) (see also the accompanying illustration) may be explained by the fact that the primary tumour contained large areas of pure seminoma like tissue, these areas were presumably the metastasizing parts The third patient, still alive and free from recurrence, had a fairly small metastasis from a malignant melanoma

Table 4

Survival in relation to the sedimentation rate at the time of treatment of the lung deposit

Sedimentation rate mm/hour	Patients		Survival (months)	
	Total	Recurrence	Mean	Median
13 or more	7	7	17	12
12 or less	13	5	5?	26

Two of the three survivors still have an easily recognizable roentgen change at the site of the original metastasis (see the roentgenograms)

Four of the patients died from a recurrence of the growth In two of these (Cases 15 and 18) a moderate decrease in the tumour size was noted initially after which no further change occurred Pulmonary resection was therefore performed in both instances about 2 1/2 and 6 months respectively after termination of radiotherapy The histologic examination revealed a small focus of residual malignant tissue (with marked regressive changes) in one patient (Case 15) no more cancer cells could be recognized in the other patient None of the patients had any other sign of metastases at the time of the chest operation however only a few weeks later both developed a fulminating recurrence of the growth

One patient with a mammary carcinoma and another with a tumour of the testis failed to benefit from radiotherapy but in both the dose to the pulmonary deposit was rather low

Discussion

The material is small and does not permit far reaching conclusions Certain observations deserve attention however

1 The testis tumour group includes 7 patients four of whom are alive and without recurrence more than 4 8 10 and 14 years respectively after treatment of the pulmonary metastases None of these had primary tumours diagnosed as seminoma three were embryonal carcinomas and one a teratoid tumour The results are surprisingly good As to the other tumour types represented in this material their individual numbers are too small to permit an evaluation

2 An increased sedimentation rate (i e more than 12 mm/hour) was evident in seven patients at the time when treatment of the pulmonary metastases was initiated All of them had a recurrence (Table 4) compared to only five of the thirteen who had a normal sedimentation rate The survival figures for these

Table 5

Survival in relation to the interval between treatment of the primary tumour and that of the metastases

Interval	Number of patients		Survival in months	
	Total	Recurrence	Mean	Median
Less than 1 year	7	5	25	12
More than 1 year	13	7	48	35

two groups seem to indicate that an increased sedimentation rate decreases the chance of survival (Table 4)

3 In Table 5, the relationship of survival to the length of time between treatment of the primary tumour and the appearance of the deposit in the lung is recorded The small number of patients prevents a proper statistical evaluation but there seems to be some indication that an interval of less than one year reduces the chances of a good result However, numerous case histories demonstrate that this rule has many exceptions

4 The discovery of a pulmonary deposit in a patient with malignant disease sometimes represents a diagnostic problem as to the underlying nature of the process In addition, the attendant physician is often reluctant to start treatment of lung metastases, generally because he considers the prognosis uncertain

The authors have somewhat arbitrarily chosen a delay of two months between the diagnosis and the treatment of the pulmonary deposit as normal, in the sense that they consider a longer period most probably the result of hesitation on the part of the subjects concerned Five of the patients had a delay of more than two months All of them died from the growth and the survival figures (both mean and median) were only half the value of the other 15 patients The authors do not believe that those five patients derived any benefit from this extra delay, rather the contrary, as the possibility of further spread of the neoplasm increased

5 The initial effect of treatment was good in five of the seven patients in the radiation group, in four of these five patients, infiltration remained roentgenographically visible and more or less unchanged after a moderate initial decrease in size following treatment Two of these patients are alive, free from recurrence and still with easily recognizable signs a long time (more than 2 and 14 years, respectively) after treatment The other two were *subjected to operation* but no active changes were evident histologically Both patients however died shortly thereafter from a massive dissemination of the disease and we feel tempted to link the surgical trauma with a disturbance of the biologic equilibrium between 'dormant' malignant cells and normal tissue This theory is sup

ported by the experimental findings of FISHER & FISHER (1959) who demonstrated that an operation can promote the growth of metastases in rats injected with cancer cells

The authors believe that the persistence of roentgenologic infiltration may be a frequent finding after irradiation of pulmonary secondaries These should therefore not be removed by surgery unless they start to increase in size

Conclusions

The experience of the authors and the available literature suggest an active attitude towards the treatment of isolated lung metastases Therapy should normally be initiated as soon as the diagnosis has been established

Surgical removal limited when possible to local excision has definitely proved its value and will therefore generally be the preferable form of treatment It seems however that radiotherapy offers a good alternative method in radiosensitive tumours and that it should be the treatment of choice in this group when the general condition of the patient is poor The persistence of changes in the lung corresponding to the irradiated tumour does not unless their size increases indicate that an operation should be performed

The prognosis is probably less favourable when the pulmonary deposit appears during the first year after treatment of the primary tumour but even then active therapy should at once be undertaken An increased sedimentation rate diminishes the chances of a good result

Subjective complaints and the ordinary clinical examination cannot be relied upon to discover secondary deposits in the lungs at a reasonably early stage these will be revealed only by periodic roentgen examinations As metastases can appear many years after the seemingly successful treatment of the parent tumour (in the material up to 12 years) these examinations should be continued for a long period

SUMMARY

Twenty patients with malignant disease were treated for isolated lung metastases 13 by surgery and 7 by radiotherapy Th survival rate after 5 years was 38 per cent and long term survivals were observed both in the surgical and radiation groups Surgical removal may usually be undertaken without great risk to the patient but radiosensitive tumours may also be treated effecti ely by irradiat on

ZUSAMMENFASSUNG

Zwanzig Falle von Lungenmetastasen werden beschrieben Dreizehn Falle wurden chirurgisch behandelt und s eben bestrahlt Die Überlebungsquote nach funf Jahren betrug 38 und sowohl in der chirurgisch behandelten als auch in der bestrahlten Gruppe wurden

langfristige Überlebungszeiten beobachtet Der chirurgische Eingriff kann gewohnlich ohne grosses Risiko fur den Patienten unternommen werden Als Alternative konnen strahlenempfindliche Geschwulste effektiv durch Bestrahlung behandelt werden

RÉSUMÉ

Vingt malades atteints d affection maligne ont été traités pour une métastase pulmonaire isolée, 13 par chirurgie et 7 par radiothérapie Le taux de survie apres 5 ans a été de 38 pour cent et on a observé de longues survies avec ces deux traitements L exérèse chirurgicale peut habituellement être faite sans grand risque pour le malade mais on peut aussi traiter efficacement par irradiation les tumeurs radiosensibles

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SUPPLEMENTARY TREATMENT OF NASOPHARYNGEAL TUMOURS WITH HIGH ENERGY PROTONS

by

S GRAFFMAN B JUNG B A NOHRMAN and R BERGSTROM

The administration of a curative dose of conventional roentgen radiation to nasopharyngeal tumours lying deep behind bony structures is not easy Supplementary irradiation of the tumour with radionuclide applicators has been used but this procedure is technically difficult and fails to ensure uniform irradiation of the whole tumour mass

The problem of administrating an adequate dose to nasopharyngeal tumours is much simplified with a high energy proton beam With a two field technique the skin dose may be kept below 40 per cent of the tumour dose and the absorption in the bony structures is in fact slightly reduced These conditions are favourable even when compared with those produced by roentgen rays from a 31 MV betatron (BERDAL & POPPE 1962)

Material This comprised the ten cases of malignant nasopharyngeal tumours admitted to the Department of Radiotherapy between 1964 and 1965 It was considered advisable in this exploratory series to give the proton dose only as a supplement to conventional roentgen therapy in order to decrease the influence of any possible unexpected biologic effect This policy obviously fails

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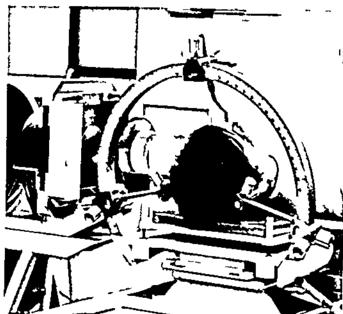


Fig 1 Subject fixed in position for irradiation The beam enters from the left through an ionization chamber a 4 cm wide circular aperture a ridge filter and a lucite absorber

to take full advantage of the geometric properties of the proton radiation field, and evaluation of the clinical results becomes more uncertain

The proton treatment was limited to the primary lesion, local metastases being treated with roentgen rays and surgery Although malignant naso pharyngeal tumours are apt to produce metastases, especially if poorly differen tiated, control and cure of the primary lesion must be the prime objective of any adequate therapy

Proton irradiation facilities The extracted proton beam from the synchro cyclotron at the Gustaf Werner Institute is monoenergetic, with an energy of 187 MeV, the beam transport system delivering a beam of about 10^{10} protons per second, focused to a cross section of a few square centimeters at the irra diation site A sharply delimited and transversely homogeneous radiation field can be obtained by sweeping the focused beam in a reticular pattern over the final aperture The dose rate depends on the cross section of the field and is about 100 rad/min for a 12 cm² field The maximum penetration depth in tissue is 23 cm By passing the monoenergetic protons through non homogeneous absorbers or ridge filters, the depth dose curve can be reshaped from the Bragg type to one having a flat plateau at the deepest region of penetration

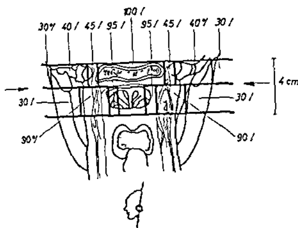


Fig 2 Schematic dose distribution from two opposing circular fields The plane of the section is indicated in the inset Rough corrections for the air cavities have been applied

The depth of the proton radiation field within the patient is easily varied by placing absorbers of different thicknesses between the ridge filter and the body

The therapeutic application of the proton beam has been described earlier by FORS et coll (1964) and KARLSSON (1964)

The dose was measured in a nitrogen flushed ionization chamber of the transmission type and with a conventional thimble chamber for double checking The proper functioning of both chambers was tested immediately before the actual therapeutic irradiation by activation dosimetry with small polystyrene cubes This method was also used for determining the transverse homogeneity of the radiation fields a variation of $\pm$ 5 per cent was considered tolerable

Dose distribution and irradiation data Two- or four field techniques were applied in the irradiation of the primary tumours with 220 kV roentgen rays A skin exposure of 400 R was given to one of the fields each day for six days a week The estimated total tumour doses are recorded in the Table The regional metastases were irradiated exclusively with 220 kV roentgen rays

The proton irradiation was performed with two opposing circular fields centered on the tumour region The tumour dose was given in fractions of 1 000 or 1 500 rad twice a week alternately from the left and from the right The choice of the individual total tumour dose was based on generally accepted clinical criteria The correct alignment of the patient was checked with a diagnostic roentgen stand equipped with an image amplifier A skull table with plugs in the auditory canals and a clamp holding the bridge of the nose restricted

Table

Clinical and physical data for cases irradiated for malignant nasopharyngeal tumours — The results of the patho-anatomical examinations were as follows: anaplastic carcinoma in Cases 2, 3, 4; poorly differentiated squamous cell carcinoma in Cases 1, 5, 6; moderately differentiated squamous cell carcinoma in Case 9; well differentiated squamous cell carcinoma in Case 8; undifferentiated tumour, probably reticulum cell sarcoma in Case 7; and solitary plasmocytoma in Case 10

Case numbers	1	2	3
Treatment of local metastases	Roentgen	Roentgen and surgery	Roentgen and surgery
Roentgen treatment completed	28 I 64	18 IV 64	12 III 64
Estimated dose (rad)	4 000	2 000	4 000
Proton treatment completed	17 IV 64	12 IV 64	20 IV 64
Total tumour dose (rad)	4 000	2 000	4 000
Number of fractions	4	2	4
Field diameter (cm)	4	4	4
Observation time after proton treatment (months)	(7)*	(20)	([illegible])
Nasopharyngeal tumour response	Transient	Good	Transient

the movements of the subject during irradiation (Fig. 1). The proton field was chosen so that the beam penetrated to a depth of 2.5 cm beyond the midline of the skull, the two fields thus overlapping in a 5 cm wide region around the midline. A schematic diagram of the proton dose distribution is given in Fig. 2.

The relative biologic efficiency (RBE) of high energy protons as compared to ^{60}Co radiation has been found to be close to 1.0 for the biologic systems tested (LARSSON & KIHLMAN 1960, BONET-MAURY et coll. 1964, FORS et coll. 1964). This value was used when the tumour dose was selected. A fraction of the dose, increasing with depth, is produced by low energy protons, however, in the ridge filtered proton radiation field. The RBE of these protons is less well known but is probably higher than 1.0. LARSSON & KIHLMAN (1960) have studied the biologic effect of the unfiltered proton field as manifested by chromosome aberrations in bean roots. Assuming that their figures are also valid for therapeutic applications, the rem dose distribution should be as depicted in Fig. 3.

Table (*cont*)

	4	5	6	7	8	9	10
	Roentgen	Roentgen and surgery	Roentgen	Roentgen	None observed	None observed	None observed
	9 IX 63	29 III 65	9 II 65	29 I 65	29 IX 64	15 X 65	29 X 64
	2 500	3 500	3 000	1 500	3 500	4 000	3 500
	7 IX 64	9 X 65	22 VI 65	2 II 65	13 XI 64	25 III 66	3 VII 64
	4 000	2 000	2 000	2 000	2 000	5 000	2 000
	4	2	2	2	2	4	2
	4	5	4	5	4	4**	4
	(10)	(3)	15	(3)	22	(1)	26
	Good	Uncertain	Good	Good	Good	Uncertain	Good

* Figures in parentheses indicate a terminated observation time

** First two fractions third and fourth fraction with 4 × 6 cm (cf text)

Results

Clinical and pathologic findings The histopathologic diagnoses of the ten cases were different Three cases (see the table) had anaplastic carcinoma and three cases poorly differentiated squamous cell carcinoma The remaining four diagnoses were (1) moderately differentiated squamous cell carcinoma (2) well differentiated squamous cell carcinoma (3) undifferentiated malignant tumour probably reticulum cell sarcoma and (4) solitary plasmocytoma

Seven cases (Cases 1 to 7) had local metastases at the commencement of the irradiation four of these (Cases 2 3 4 and 7) were later found also to have distant metastases in every instance involving the liver General extension upwards proved fatal in Case 1 seven months after proton treatment no autopsy was performed Case 5 was lost to follow up after a few control examinations the disease was reported to have terminated fatally Case 6 has been followed up for 15 months and has had no recurrence or general spread The three cases with no obvious metastases at the commencement of therapy

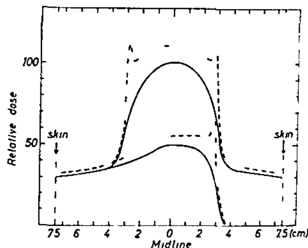


Fig 3 Central axis depth dose curves for the ridge filtered proton beam The lower curves give the rad (———) and rem (— — —) dose for a single field while the upper curves indicate the total dose from the two opposing fields

(Cases 8, 9, and 10) have presented no evidence of general spread of the disease

Discussion

Since the field of proton irradiation included only the primary tumour with surrounding tissues, the discussion will be confined mainly to the radiation effect in this region

Good regression of the primary tumour, i e disappearance of the mass and no obvious regrowth, occurred in six cases (Cases 2, 4, 6, 7, 8, and 10) No viable tumour cells were found at biopsy or autopsy

The local response was uncertain in two cases Case 5 was lost to follow up after one month of observation, during which period the tumour continuously regressed The other case (Case 9) had an extensive growth which appeared to be located in the nasopharyngeal region This was irradiated with two doses of 1 500 rad through circular fields, 4 cm in diameter Malignant tissue appeared later in the oropharyngeal region, including this region additional treatment was given with $2 \times 1\ 000$ rad through 4 cm $\times$ 6 cm fields Histologic biopsy from the nasopharyngeal region revealed no viable cancer cells The oro pharyngeal growth was then further controlled by being irradiated with $2 \times 1\ 000$ rad applying fields of irregular cross section The outcome proved fatal one month after the last treatment no autopsy was performed

Two cases failed to register good local response, they were both in an ad vanced state of the disease at the start of the radiotherapy Case 1 had an exten sive necrotic tumour which grew rapidly and soon expanded into the hypo pharyngeal region and also penetrated the skin The growth in Case 3 involved the base of the skull

The radiation effects on the normal mucous membranes and on the malignant tissue were similar as after irradiation with 220 kV roentgen rays at the same dose level A strict comparison is impossible at this stage Marked changes in the blood picture were absent Three patients suffered impairment of hearing following the proton therapy an effect that was largely transient and undoubtedly a sequel to obstruction of the Eustachian tube Audiograms revealed no significant nerve involvement

Rupture of the right carotid artery within the irradiated region proved fatal in Case 4 This case had also been treated not only by roentgen rays but also by fenestration and cauterization of the tumour preceding proton irradiation Histologically verified recurrence of the tumour had been observed at the commencement of proton treatment Following the treatment a sequestrum was present at the site of recurrence although the reaction of the mucous membranes was normal The sequestrum withstood all efforts at local treatment The autopsy material from the irradiated region was examined carefully no viable tumour cells were observed but marked cell degeneration was present in the region between the rupture and the sequestrum and massive invasion of inflammatory cells was also evident Only slight changes were observed in the corresponding contralateral region It would therefore appear that the radiation treatment cannot have been the primary cause of the rupture

Conclusions

The geometric properties of the ridge filtered high energy proton beam are obviously of advantage in the treatment of nasopharyngeal tumours The good local response and the absence of significant untoward effects in this series indicate that in future the effects of high energy protons when used exclusively should be studied Efforts to employ proton treatment to the best advantage will be directed to the relation between the radiologic response and the total tumour dose field size and dose fractionation scheme The proton beam may also be applied satisfactorily to local metastases especially to those in the retropharyngeal region as well as to well localized distant metastases since the integral dose can be kept low and adjacent critical organs avoided

Acknowledgements

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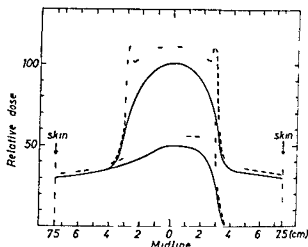


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PROGNOSIS OF RETINOBLASTOMA TREATED AT RADIUMHEMMET 1926—1963

by

B JEREB E KOCH and P E ÅSARD

The retinoblastoma is the most common form of intraocular malignant tumours in children It was first described by VIRCHOW in 1864 as a glioma and later by WINTERSTEINER (1897) as a neuroepithelioma The term retinoblastoma was suggested by VERHOEFF in 1921 and was adopted by the American Ophthalmologic Society in 1926

Although of low incidence (one in 34 000 children is born with retinoblastoma WELLER 1941) the retinoblastoma is an extremely interesting tumour for it is the only embryonic neoplasm with a markedly hereditary proclivity The exact mode of its transmission is not known although there is evidence of its being transmitted as a dominant trait Clinically it generally makes its appearance prior to the second year of age

Retinoblastomas derive from neuroepithelial tissue The tumours are classified into two groups on the basis of their degree of differentiation (1) undifferentiated retinoblastomas and (2) differentiated retinoblastomas characterized histologically by the formation of true rosettes

The growth originates from single or from multiple foci in the retina of one

Submitted for publication 11 July 1966

SUMMARY

Ten cases of malignant nasopharyngeal primary growths were treated by high energy protons in addition to 220 kV roentgen irradiation The physical properties of proton radiation are briefly discussed Six of the cases responded well to the treatment and no signs of local recurrence appeared during the relatively short period of observation The response was uncertain in two cases and local growth continued in two cases

ZUSAMMENFASSUNG

Zehn Fälle von bosartigen Primartumoren des Nasopharynx wurden mit 220 kV Rontgen strahlung und ausserdem mit hochenergetischen Protonen behandelt Eine kurze physikalische Beschreibung der Protonenbestrahlung wird angegeben Sechs der Fälle reagierten gut auf die Behandlung und keine Zeichen lokaler Rezidive konnten wahrend der verhaltnismassig kurzen Observationszeit festgestellt werden Der Effekt der Behandlung war unsicher in zwei Fallen und in zwei anderen Fallen wurde Wachstum des Tumors konstatiert

RÉSUMÉ

Dix cas de tumeurs malignes primitives nasopharyngiennes ont été traitées par les protons de haute énergie en plus de la roentgen thérapie à 220 kV Les auteurs examinent les propriétés physiques du rayonnement protonique Six de ces cas ont bien réagi à ce traitement et n ont pas présenté de signes de récidive locale pendant la période relativement courte d observation L effet de ce traitement a été incertain dans deux cas et la tumeur a continué à croitre dans deux cas

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In all patients except one who was irradiated preoperatively the diagnosis was confirmed histologically In order to classify the tumours according to the degree of differentiation the specimens were re examined 30 specimens of the 35 patients treated by radiotherapy being available for re examination Tumours with more than one true rosette formation per microscopic slide were classified as differentiated and all other tumours as undifferentiated Eighteen tumours in this series have been classified as undifferentiated and twelve as differentiated

Treatment Radiotherapy was administered to the patients for one or more of the following reasons (1) the parents refused surgery (2) the operation was doubtfully radical, (3) locally recurrent disease, and (4) involvement of both eyes

Eight of the 12 patients with unilateral involvement received radiotherapy When the growth was bilateral however the eye with the more advanced disease was enucleated and the other eye irradiated Twenty seven of the 29 patients with bilateral involvement received radiotherapy, in three patients, radiotherapy was withheld due to advanced disease

Conventional roentgen treatment was used until 1959 The factors were 170 kV 0 5 mm Cu filter 40 cm FSD the dose being delivered through a temporal and a frontal portal the latter directly covering the eye Beginning in 1950 however the frontal portal was moved medially over the root of the nose to afford better protection to the anterior portion of the eye Special treatment cones made of tin and of the same type as described by REESE (1953) have been used (Fig 1) The field sizes ranged from 2 5 to 4 cm in diameter The exposure was usually 200 R three times a week There was a great deal of variation in the total radiation dose and fractionation The tumour doses have been calculated retrospectively

In order to evaluate the dose distribution obtained with the irradiation technique used it was necessary to determine the isodose diagrams for the cones For this purpose a small commercial silicon photodiode (Siemens BPY 11 size 4 8 × 2 2 × 0 9 mm) coated with epoxy resin and connected to a DC microvolt ammeter was used The energy dependence of this diode at 170 kV roentgen rays has been investigated previously and is expected soon to be published (ÅSARD & BAARSEN 1968) It was then shown that the errors introduced are negligible when measurements are performed in a homogenous phantom All our measurements of isodo e diagrams were carried out in a water phantom

Reconstruction of a typical treatment based on the isodose diagrams is shown schematically in Fig 1 Larger fields were used in some cases but this

or both eyes A quarter to one third of all retinoblastomas are bilateral (REESE 1953, DARGEON 1960) There need be no involvement of the optic nerve, not even when both eyes are affected

The tumour spreads either directly into the meningae, or reaches the intra cranial space via the optic nerve It may also reach the choroid, either directly or by implant, and metastasize from there Distant metastases are primarily located in the skeleton, although the lungs, liver and other organs may also be involved Death is caused by intracranial invasion in slightly more than 50 % of cases (ANDERSSON 1961, REESE 1953)

Material Forty one patients with retinoblastoma, 22 males and 19 females, were seen at Radiumhemmet in the years between 1926 and 1963 The age of the patients ranged from two months to 12 years

An adequate family history was obtained in 24 patients One of these pa tients had a twin sister who was also affected, while three patients had a parent or an ancestor with the disease A brief history of these three patients is thought to be of interest

Case reports

Case 1 Second daughter of a woman who had had the left eye enucleated for retino-blastoma at the age of 4 years The patient s sister her mother s first child died of retino blastoma after both eyes had been enucleated The patient was found to have bilateral retinoblastomas when she was 7 months old Enucleation of one eye and radiotherapy of the other had little effect The patient died two years after treatment

Case 2 Boy whose father had had both eyes enucleated for retinoblastoma at the age of 18 months The boy also had tumours on both sides and was treated with enucleation and radio therapy at the age of 10 months This patient has not been followed up

Case 3 Boy whose grandfather had had both eyes enucleated as a baby for retinoblastoma and whose *father had one eye enucleated and was treated with radiotherapy also for retinoblas toma* In our patient a tumour was present in the left eye at the age of 4 months His parents then insisted upon treatment with roentgen radiation alone Ten months later a tumour was discovered *in the right eye and this was likewise treated with roentgen* During the next 5 years several roentgen treatments were given to both eyes for recurrences In August 1951 the left eye was enucleated The patient has since that time been well and free from neo plasm He has however been operated upon for a cataract of the right eye and wears correc tive lenses The tumour in the left eye proved histologically to be a highly differentiated retinoblastoma with rosette formation

Of the 41 patients studied, twenty nine had bilateral involvement while the remaining twelve had unilateral tumours One patient has been lost to follow up

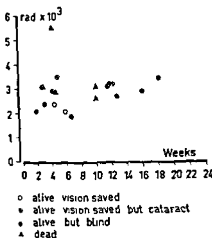


Fig 2 Tumour doses fractionation and the results of treatment of 2[illegible] patients with retinoblastoma

One patient has died since the other two patients have survived to date Of the four patients with unilateral tumours who were treated for local recurrence only one survived more than 5 years

Of 27 patients with bilateral growth sixteen are alive and free from the disease twelve of these patients having survived for more than 5 years In seven of the 16 surviving patients bilateral enucleation was eventually required due to the progression of the tumour In the remaining nine patients the surviving eye was saved In five of these patients however a post irradiation cataract developed with various degrees of impaired vision In five of the 27 patients with bilateral involvement a growth was discovered in the second eye after the first eye had been enucleated One of these patients has died Two of these patients are alive more than 5 years after the enucleation of the second eye and two patients are alive with cataracts and corrected vision after 3 years and 14 years respectively (Table 2)

The relation between dose and cure rate is shown in Fig 2 for those patients in whom the tumour dose could be calculated in retrospect

Of the 15 patients who died of retinoblastoma nine died during the first year after treatment four died during the second year one died during the third year and one patient died during the fourth year

Prognosis The prognosis for the patients with retinoblastoma in this series appeared to be equal for both sexes and did not apparently, depend upon the age of the patient

In order to estimate the influence of the type of tumour and of its exten

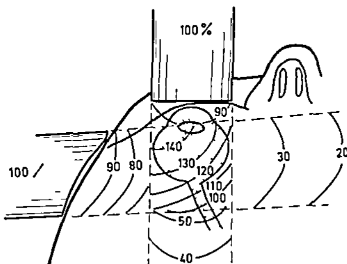


Fig 1 Dose distribution in the eye at roentgen treatment with 170 kV and 0 5 mm Cu filter The isodose curves are indicated in per cent of the dose given to each portal

did not lead to any significant change of the dose distribution in the eye No correction for specific bone absorption was made because most of the patients were about one year old The average dose to the eye is given as the tumour dose, the inhomogeneity factor being about ± 15 % This does not mean, of course, that the absolute values of the tumour doses indicated in Fig 2 are correct It was not possible, however, to determine the error in each individual case

Fig 1 also shows that the direction of the temporal field is critical for the dose to the lens If the temporal field goes through the lens, the dose will be as high as 140 % If the field is directed below the lens, the dose to the lens will be about 90 %

During the last few years some patients have been treated with a 12 MeV electron beam by a cross fire technique using two or three frontal fields The anterior parts of the eye were protected by a special shield, as described by HULTBERG et coll 1965 The usual tumour dose was about 3 200 rad over about four weeks

Intra arterial chemotherapy with TEM (triethylenmelamine) has been attempted in a few advanced cases and in combination with radiotherapy

Results

Four of the eight patients with a unilateral tumour who were treated by surgery and radiotherapy survived 5 years or more without recurrence One of these four patients had been irradiated preoperatively at operation no sign of growth was apparent in the specimen obtained Three patients received postoperative radiotherapy because the operation was doubtfully radical

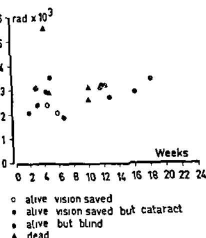


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Table 1

Results in eight patients with unilateral tumours

	Number of patients who died	Alive and well more than 5 years
Preoperative radiotherapy plus enucleation	0	1
Enucleation plus postoperative radiotherapy	1	2
Local recurrence	3	1

Table 2

Results in twenty seven patients with bilateral tumours

Deaths	Alive more than 2 years	Alive more than 5 years	Alive but blind (bilateral enucleation)
11	16	12	7

sion, on the prognosis, the material has been analysed according to the following criteria (1) extraocular growth, (2) extraretinal growth subdivided into (a) extension into the optic nerve beyond the lamina cribrosa but totally extirpated, and (b) extension into the choroid Implantations in the retina and the anterior chamber have been placed in the group intraretinal tumour (see Table 3)

Discussion

Since retinoblastoma is a rather uncommon tumour our knowledge of its behaviour is necessarily limited From the therapeutic point of view much is open to discussion and further experience is needed At present, the treatment of choice of unilateral growths is enucleation The condition is usually so far advanced that the delay in effective treatment caused by an attempt to irradiate the tumour seems to be unjustified in view of the usually imminent brain invasion The safety margin of the resected optic nerve should be at least 10 mm Radiotherapy should follow if there is any doubt of the operation not having been radical enough In cases of bilateral growths, enucleation of the more affected eye is usually performed and an attempt made to save the other eye with some degree of vision by means of radiotherapy

There is no uniform way of treating retinoblastoma by irradiation mainly because the optimal dosage is not known Locally applied sources of radioactivity are being used and recommended by some (STALLARD 1918 Ro

Table 3

Outcome of the treatment in the different groups of patients

	Differentiated	Undifferentiated	Extra ocular	Extension into optic nerve	Extension into choroid	Intra retinal
Dead	?	9	7	0	7	3
Living	10	9	1	4	6	9
Total	1?	18	8	4	13	12

SENGREN et coll 1963) though the method lends itself to the treatment of small localized tumours In view of the fact that retinoblastoma often has multilocular origin, it would seem necessary *to deliver a homogenous dose of* radiation to the whole eye with adequate protection of the lens and cornea

REESE *used a 200 kV roentgen unit* and delivered about 4 000 R to each of two portals in about 15 weeks He started by administering twice this dosage but his patients developed a high percentage of complications mainly in the nature of vitreous hemorrhage Some cures published in the literature have been achieved with surprisingly low dosage Our results indicate that within the range given the tumour dose has little influence on the cure rate Electron beam therapy has been used by the present authors only during the last six years in 8 patients With electron beam therapy a fairly homogenous dose distribution in the eye can be obtained, with low doses to the lens

The cure rate for retinoblastoma as reported by HIRSCHBERG in 1869 was 6.5 % By WINTERSTEINER in 1897 it was 13 % *In recent years with more* adequate surgery and radiotherapy the results have improved markedly

REESE reported that 63 2 % of the patients lived and were without recurrence 5 years after treatment this is comparable to the present results

Better results with the more highly *differentiated* tumours have been reported and this was confirmed in the present series DAS (1964) reported only 6 highly differentiated tumours *with rosette* formation in 140 patients 35 of these with bilateral tumours were adequately followed and none survived

As to the extension *of the tumour* the general impression that growth into the choroid renders the prognosis worse could not be confirmed in the present material Neither has *the* involvement of the optic nerve influenced the prognosis unfavourably provided the neoplasms were radically extirpated

The results *are* obviously improved by systematic co operation between surgeon and radiotherapist and also by an early diagnosis The value of chemotherapy *remains unestablished*

SUMMARY

A review of the results of the combined treatment by surgery and radiotherapy in a material of 35 patients with retinoblastoma between 1926 and 1963 is presented

ZUSAMMENFASSUNG

Ein Überblick uber die Resultate der kombinierten chirurgischen und Strahlentherapeutischen Behandlung des Retinoblastomes an einem Material von 35 Patienten die zwischen 1926 und 1963 behandelt wurden wird gegeben

RÉSUMÉ

Présentation d une étude rétrospective des résultats du traitement associé chirurgical et radiothérapique sur 35 malades atteints de rétinoblastome entre 1926 et 1963

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POTENTIATION OF RADIATION EFFECT ON FEET OF MICE AFTER PROLONGED APPLICATION OF A TOURNIQUET

by

GEORGE CRILE JR and ANTONIO RODRÍGUEZ ANTUNEZ

The literature on the potentiation of radiation by heat was summarized in a previous report (CRILE JR 1963) and experiments were reported, in which exposure of the feet of mice to temperatures of 44° C for from half an hour to *one hour, greatly increased the destructive effects of radiation* It made no difference whether radiation was given immediately before during, or immediately after, the heating, but if the heating and the radiation were separated by more than a few hours much of the potentiation of the radiation was *lost* Not only was the biologic effect of the radiation increased by heating but also the time between exposure to radiation and the appearance of the radiation effect was shortened

These observations suggested that the potentiation of the radiation effect by heating represented something more than a summation of two types of injuries and implied that there was a true synergism between heat and radiation The purpose of this paper is to report a similar potentiation of the de

Submitted for publication 7 July 1966

Table 1

Relationship between damage of feet (permanent deformity such as loss of toes, fusion of toes, or loss of foot) and radiation dosage (normal Swiss mice)

Single dose in R	Proportion of number of feet damaged	Percentage of feet damaged
1 500	0/6	0
1 800	6/58	10
2 000	7/16	44
2 500	11/16	69
3 000	32/32	100

structive effects of radiation on the feet of mice, when the circulation to the feet is interrupted for several hours by application of a tourniquet either before, during, or after the radiation. As in the case of heat, much of the potentiation was lost when the period of interruption of circulation and the time of exposure to radiation were separated by more than a day. Again, as in the case of heat, the period between exposure to radiation and appearance of the radiation effect was shortened by prolonged application of a tourniquet.

Materials and Methods. Female Swiss mice six weeks old were restrained as previously described (CRILE) with the left hind foot of each mouse protruding through a slit in sheet lead, and the body shielded under the lead. The feet were irradiated in a single exposure under a 200 kV machine operating at 20 mA. The HVL was 0.4 cm of copper, target skin distance 20 cm, and the dosage rate was 35 R per minute calculated in air.

Exposures of 2 000 R in a single dose resulted in permanent damage to the feet of some mice, but caused no deformity in the majority, while 2 500 R damaged the feet of most of the mice, and 3 000 R caused irreversible damage or complete destruction of the feet of almost all the mice. The extent of damage after various doses is shown in Table 1. The condition of the feet was recorded 30 days after completion of the treatment.

Anoxia was induced by applying a heavy rubber band tourniquet to the fleshy part of the leg just above the foot. The band was tied tightly enough to prevent all arterial bleeding. When the tourniquet was left in place two hours or less and then removed, erythema and edema developed, but there was no irreversible damage of the foot. Four hour to six hour occlusions occasionally caused deformities, but most of the feet incurred no irreversible damage. After six hour occlusion, permanent damage was evident in two of 33 feet (6 %).

Permanent damage from occlusion by tourniquet was always apparent within

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Table 2

Relationship between occlusion and radiation effect on feet of normal Swiss mice

Treatment	Proportion of mice with damaged feet	Percentage of mice with damaged feet
Tourniquet 4 hours	1/24	4
1 800 R	6/58	10
Tourniquet 4 hours followed by 1 800 R	45/57	79
1 800 R followed by tourniquet 4 hours	16/18	88
Tourniquet 4 hours 1 800 R in middle of period of occlusion	12/12	100

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Tourniquet 6 hours followed by 1 800 R	28/39	72
1 800 R followed by tourniquet 6 hours	27/39	69
Tourniquet 6 hours with 1 800 R given in middle of period of occlusion	27/29	93

a week and could be evaluated before the feet began to show reaction to irradiation Damage to the feet consisted in clubbing due to skin reaction of toes, plus adherence to one another When damage is greater, the foot sloughs off

Results

Effect of tourniquet and radiation on normal feet In ten separate experiments, involving 6 to 12 mice in each group of each experiment, tourniquets were left in place from 4 to 6 hours and the feet were irradiated Application of tourniquets increased the destructive effects of the irradiation, as shown in Tables

Table 4

Relationship between irreversible damage to feet of normal Swiss mice and interval between tourniquet occlusion and exposure to radiation — Tourniquets applied 4 hours — Radiation exposure 1 800 R

Treatment	Proportion of mice with damaged feet	Percentage of damaged feet
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Radiat on 4 days after tourniquet occlusion	(/29	21
Radiati n only	2/24	8
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When the tourniquets were applied for two hours or less and 1 800 R was given little or no potentiation of the radiation effect was observed When circulation was occluded for four hours and the feet received 1 800 R the majority of feet were damaged but the damage was no greater when the feet were given 1 800 R after 6 hours of occlusion than after 4 hours (Tables 2 and 3) In fact 80 % of 87 feet treated by 1 800 R and 4 hours of occlusion were damaged compared with 77 % of 107 treated by the same dose of radiation and 6 hours of occlusion If radiation was not given soon after the period of occlusion much of the potentiation of the radiation was lost The results of a series of experiments in which the intervals between application of tourni quet and radiation were increased up to 4 days are shown in Table 4

Time of appearance of radiation reaction When a tourniquet was applied for four hours immediately before during or immediately after the foot was exposed to 1 800 R not only was the amount of radiation damage increased but also the time between exposure to radiation and appearance of radiation reaction was shortened In controls radiation reaction appeared 18 to 21 days after treatment averaging 20 days In ten separate experiments each involving 6 to 10 mice treated by tourniquets for from four to six hours with from 1 800 R to 2 000 R the time of appearance of the radiation reaction was 13 12 11 1? 11 12 11 10 10 10 days averaging 11 5 days

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Effect of tourniquet and radiation on tumors The radiosensitivity of tumors (S91 melanoma in DBA, or BDF hybrid mice and T241 in C57 mice) implanted

Table 5

Melanoma S91 on feet of BDF hybrid mice ($B_6D_2F_1$) (moderately radiosensitive tumor) (cure = no tumor three months after treatment)

Treatment	Results
Tourniquet 6 hours	0/ 8 cured
1 000 R	0/ 8 cured
Tourniquet 6 hours 1 000 R given with tourniquet on	12/18 cured
2 000 R	11/14 cured

on the feet of mice was increased by application of a tourniquet for four hours before irradiating the tumors, but the tumor's increase in radiosensitivity did not seem to be any greater than that incurred by the normal tissues of the foot As a result, those tumors that were curable by moderate doses of radiation, without damage to the feet, became curable with lower doses after a tourniquet had been applied This phenomenon was of no advantage from the standpoint of treatment because the therapeutic ratio seemed to remain unchanged The results are given in Table 5

When T241 on the feet of C57BL mice was treated with 2 000 R its growth was not controlled (0/8) With 2 500 R the tumor was cured in 10/24, but in eight of the ten cured mice the foot was destroyed Thus, at doses of 2 000 to 2 500 R only 2/32 mice were cured without damage to their feet When a tourniquet was applied for four hours and 1 200 R was given, the results were even worse — none of the 30 mice were cured without damage to their feet

Discussion

After prolonged application of a tourniquet to the thigh there appeared to occur a change in the tissues of the feet, making them more radiosensitive and shortening the time between exposure and the appearance of reactions The potentiation of the radiation effect may be merely a summation of the effects of two different types of injuries, but the shortening of the time between exposure and appearance of reaction is not explained Neither is it clear why 2 hour occlusion gives no potentiation of the radiation reaction, 4 hour occlusion a maximum potentiation, and 6 hour occlusion gives no more than does four hours

In order to rule out simple inflammation as a cause of the above changes, the feet of the mice were injected with various inflammatory agents including alcohol, turpentine, croton oil, serotonin, histamine, and extracts of inflamma

tory tissues (heated tissues and inflammatory exudates from Selye's pouch (supplied through the courtesy of the Armour Pharmaceutical Company, Kankakee Illinois) The feet were then irradiated but in none was there any potentiation or acceleration of the reaction

Inasmuch as heat and tourniquet occlusion potentiate radiation only when they are applied shortly before, during, or shortly after the radiation and lose most of their effects when the time intervals between the treatments are longer than one day it seems that they act by means of enhancing the radiation effect rather than by merely adding one type of injury to another Since there is no obvious explanation for this enhancement or for the shortening of the time between exposure and appearance of radiation effect these phenomena should be studied further

This experiment seems to dim the hope of ELLIS (1962) that hypooxygenation would produce the death of cells already poorly oxygenated and thus increase the therapeutic ratio by eliminating the cells that were hyposensitive to radiation Our results demonstrate that prolonged hypoxia does not increase the therapeutic ratio between malignant and normal tissue as proposed by GRAY (1962) for shorter periods of hypoxia

SUMMARY

The destructive effects of irradiation were increased by the application of tourniquets to legs of mice The time between radiation exposure and appearance of irradiation reactions was shortened when a tourniquet was applied for four hours immediately before during or immediately after irradiation When the time between occlusion and irradiation was longer than one day much of the effect of occlusion was lost implying a synergistic rather than additive relationship Inflammatory agents did not increase the destructive effects of radiation

ZUSAMMENFASSUNG

Der zerstorende Effekt der Strahlung wurde erhoht wenn ein Tourniquet an den Fussen von Mausen angelegt wurde Das Intervall zwischen der Bestrahlung und dem Auftreten von Reaktionen wurde kurzer wenn das Tourniquet vier Stunden lang entweder unmittelbar be or oder wahrend oder unmittelbar nach der Bestrahlung angebracht wurde Wenn das Intervall zwischen der Okklusion und der Bestrahlung langer als einen Tag war so wurde der Okklusions Effekt beschrankt was eher auf ein synergistisches Verhaltnis als auf einen additiven Effekt deutet Die *zerstorende Einwirkung der Bestrahlung* wurde nicht bei Verwendung entzundlicher Agensen erhoht

RÉSUMÉ

L effet destructeur des radiations est augmenté par l application de garrots sur les pattes des souris L intervalle de temps entre l exposition aux radiations et l apparition de réaction dues aux radiations est raccourci quand on a appliqué un garrot pendant quatre heures

ımmédıatement avant pendant ou ımmédıatement après l ırradıatıon Quand ıl y a plus d un jour entre l applıcatıon du garrot et l ırradıatıon la majeure partıe de l effet du garrot faıt défaut ce quı ımplıque qu ıl y a plutot synergıe qu addıtıon de leur effets Les agents ınflammatoıres n augmentent pas les effets destructeurs de l ırradıatıon

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FROM STATENS INSTITUTT FOR STRÅLHYGIENE, OSLO, NORWAY

RADIATION LOAD TO THE GONADS IN DIAGNOSTIC AND THERAPEUTIC PROCEDURES

by

K. KOREN, S. MAUDAL, J. FLATBY and L. BERTEIG

Investigations have been carried out in many countries in recent years to evaluate the genetic hazards to the population from the medical use of ionizing radiation and the literature on the subject has become quite comprehensive. Attention has mainly been focused on the use of roentgen rays in diagnostic procedures, however, since these are the ones that generally give the highest contribution to the genetic radiation dose. Data and investigations on such contribution from therapeutic procedures are not so numerous but the results obtained indicate what generally has been expected, namely that it is much lower than in diagnostic radiology.

General methods and instrumentation. The genetically significant radiation dose or shorter expressed, the genetic dose, may be assessed when the following information is available: the average radiation dose to the gonads from each type of examination and treatment, the number of examinations and treatments of each type, the age group and sex, the number of individuals in the population, and the child expectancy factor as a function of age and sex (United Nations Scientific Committee on the Effects of Atomic Radiation

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Table 1

Child expectancy factor in Norway 1958

Age group	Male	Female
0—14	2 66	2 86
15—19	2 65	2 82
20—24	2 50	2 33
25—29	1 85	1 43
30—34	1 12	0 73
35—39	0 58	0 29
40—44	0 23	0 065
45—49	0 09	0 006
50—54	0 028	0
55—59	0 0086	0
> 60	0 0010	0

1962). The number of individuals in the population in terms of age and sex is obtained from the official statistics and the child expectancy factor has been calculated from data given here. The values applied refer to 1958.

The genetic dose G is calculated by means of the formula

$$G = \frac{\Sigma D_{i\,k} \; P_i \; n_{i\,k}}{\Sigma P_i \; N_i}$$

$D_{i\,k}$ is the average gonad dose per examination/treatment of type k for subjects of age group i, and $n_{i\,k}$ is the number of examinations/treatments of type k performed in those belonging to age group i, P_i is the child expectancy factor (Table 1) and N_i is the number of subjects in the whole population, both referring to age group i. The summation must be carried out for both sexes and the foetus.

The denominator is assessed to a value of 4 530 000 for the Norwegian population of 1958, including the foetuses. This value is used in all calculations of the genetic dose, both in diagnosis and therapy.

Information on the annual number of examinations/treatments $(n_{i\,k})$, were not available from official statistics, and collection of the necessary data had to be performed as part of the investigation. The methods applied and the results obtained, for diagnostics and therapy respectively, will be dealt with in the subsequent paragraphs.

The gonad dose measurements were carried out with the Kondiometer from the 'Physikalisch Technische Werkstatten' in Freiburg. The ionization

Table 2

Number of examinations at hospitals and private roentgen institutes in Norway 1958

Institution group	Recorded examinations	Estimated additional examinations	Estimated total examinations	Distribution according to type of examination	Distribution according to age and sex
Hospitals with roentgen department	721 000	10 000	731 000	427 000	63 000
Private roentgen institutes	60 000	33 000	93 000		
Smaller hospitals	70 000	21 000	91 000	13 500	
Total	851 000	64 000	915 000	440 [illegible]00	63 000

chambers were calibrated against our standards in roentgens thus giving the exposure The transformation of exposures to corresponding values of the dose equivalent in rems was accomplished by means of the conversion factors 0 93 and 0 94 for roentgen diagnostics and therapy respectively (NBS Handbook No 85)

An anatomical phantom was constructed and used for gonad dose measurements in therapy and to some extent also in diagnostics (DEVIK FLATBY & BERTEIG 1960) The phantom was also suitable for assessing the effect of various shielding devices and shielding methods and for determining the factors transforming rectal doses into ovary doses

Roentgen diagnostics

Statistical data on the number of examinations Questionnaires were sent to all establishments in Norway where roentgen examinations are performed Information on total number of examinations distribution with regard to examination type and film consumption were requested Replies were received from almost all the establishments in question but with a varying degree of completeness Table 2 includes a survey of the data obtained from hospitals and private roentgen institutes establishments covering all or most types of examination

The estimated number of unrecorded examinations and the estimated total number of examinations are also given in the table The error in the estimated total number of examinations should be relatively low of the order of 2 to 3 % The distribution with regard to type of examination was recorded

Table 3

Estimated number of roentgen examinations and sex/age distributions in Norway 1958 — The sex/age distribution is given as a percentage of the total number of examinations for both sexes

Type of examination	Total *number*	0—1 years		2—4 years	
		M	F	M	F
Chest heart lung	647 000	0 70	0 49	1 17	1 71
Mass chest civil	577 000				
Mass chest military	167 640				
Femur	10 000	0 28	0 17	1 13	0 59
Hip	33 000	0 29	0 52	0 88	1 52
Pelvis	40 800	0 43	1 10	1 30	0 79
Lumbosacral spine	74 300	0 14	0 18	0 14	0 07
Urography	25 700	0 44	0 25	0 32	0 63
Urethrocystography	1 500	0 20		0 10	
Stomach	90 100	0 76	0 34	0 12	0 09
Colon	22 600	0 95	0 32	0 82	0 12
Abdomen	72 000	0 79	0 50	1 87	0 62
Pelvimetry and abd obst	1 800				
Hysterosalpingography	1 270				
All other (not dental)	420 000				
Total (not dental)	2 134 000	Population of Norway appr 3 500 000			

for about 50 % of the examinations belonging to the category collected in Table 2 From this information a mean distribution was calculated for hospitals with roentgen department and private roentgen institutes and smaller hospitals, respectively These distributions were used in cases where no or few data other than the total number of examinations were given in the questionnaires

The distribution of the examinations in terms of sex and age groups could not be directly supplied from any hospital or other establishment A retrospective counting of some 63 000 examinations in four hospitals was therefore arranged, and the registration was particularly concentrated on those types of examination that are known to be of importance for the genetic dose The age and sex distributions thus determined were used in the calculations of this dose

For civil and military mass chest examinations a complete recording of the total number of examinations was achieved For the civil mass chest examinations the age/sex distribution was based on general population statistics The

Table 3 *(cont.)*

5—9 years		10—14 years		15—19 years		20—24 years		25—29 years	
M	F	M	F	M	F	M	F	M	F
1 75	1 42	0 70	0 57	1 13	0 95	1 30	1 61	2.20	2 72
		5 47	5 17	4 01	3 86	3 51	3 36	3 79	3 62
						71 4		17 9	
4 91	1 79	6 40	2 96	4 22	0 88	5 24	0 55	2 66	0 52
1 98	1 11	1 22	1 28	0 81	0 84	1 16	0 41	1 05	1 16
2 16	0 90	2 29	2 39	1 25	1 25	1.25	1 50	1 50	1 25
0 35	0 11	0 91	0 42	1 87	1 87	3 17	2 08	2 71	1 69
1 13	1 77	1 00	0 88	1 07	1 49	1 63	1 85	2 88	2 58
0 10		0 10		1 12		0 75		1 49	
0 13	0 14	0 40	0 22	0 72	0 64	2 36	1 12	2 42	1 80
0 19	0 44	0 57	0 63	0 38	0 38	0 88	0 95	1 39	1 52
1 61	1 16	2 07	1 82	1 12	2 15	2 15	2 24	2 57	3 19
							17 65		29 40
					1 0		5 0		16 0

examinations performed in the Military Services were of course treated separately since a few age groups predominate in these services

The estimated annual number of roentgen examinations in Norway (1958) and the applied age/sex distribution are given in Table 3 The number of examinations performed in each age group and sex is given as a percentage of the total number of examinations of each kind

Gonad dose measurement The testis dose was measured by attaching the ionization chamber to the scrotum and the ovary dose by introducing the chamber into the rectum of the patient A description of the methods applied for measuring ovarial doses was given in an earlier publication (DEVIK FLATBY & BERTEIG 1960) In addition to the doses recorded in the patients in the course of the examinations phantom measurements were also carried out The latter were used particularly for assessing ovary doses when measurement in the patients was difficult to achieve In small girls the ovary dose was calculated from the resulting skin dose The number of complete sets of measurements either in

Table 3

Estimated number of roentgen examinations and sex/age distributions in Norway 1958 — The sex/age distribution is given as a percentage of the total number of examinations for both sexes

Type of examination	Total number	0—1 years		2—4 years	
		M	F	M	F
Chest heart lung	647 000	0.70	0.49	1.17	1.71
Mass chest civil	*577 000*				
Mass chest military	167 640				
Femur	10 000	0.28	0.17	1.13	0.59
Hip	*33 000*	*0.29*	*0.52*	*0.89*	*1.52*
Pelvis	40 800	0.43	1.10	1.30	0.79
Lumbosacral spine	74 300	0.14	0.18	0.14	0.07
Urography	*25 700*	*0.44*	*0.25*	*0.32*	*0.63*
Urethrocystography	1 500	0.20		0.10	
Stomach	90 100	0.76	0.34	0.12	0.09
Colon	*22 600*	*0.95*	*0.32*	*0.82*	*0.12*
Abdomen	22 000	0.79	0.50	1.87	0.62
Pelvimetry and abd. obst.	1 800				
Hysterosalpingography	*1 270*				
All other (not dental)	420 000				
Total (not dental)	2 134 000	Population of Norway appr. 3 500 000			

for about 50 % of the examinations belonging to the category collected in Table 2. From this information a mean distribution was calculated for hospitals with roentgen department and private roentgen institutes and 'smaller hospitals', respectively. These distributions were used in cases where *no* or few data other than the total number of examinations were given in the questionnaires.

The distribution of the examinations in terms of sex and age groups could not be directly supplied from any hospital or other establishment. A retrospective counting of some 63 000 examinations in four hospitals was therefore arranged, and the registration was particularly concentrated on those types of examination that are known to be of importance for the genetic dose. The age and sex distributions thus determined were used in the calculations of this dose.

For civil and military mass chest examinations a complete recording of the total number of examinations was achieved. For the civil mass chest examinations the age/sex distribution was based on general population statistics. The

Table 3 *(cont)*

45—49 years		50—54 years		55—59 years		> 60 years		Total	
M	F	M	F	M	F	M	F	M	F
4 07	3 80	4 90	2 96	5 15	3 93	18 55	18 60	53 40	46 61
4 17	4 12	3 67	3 81	3 29	3 56	8 53	10 15	49 47	50 63
								98 8	1 2
2 74	2 01	3 21	3 10	2 49	4 37	9 17	29 42	50 00	50 00
2 80	27	4 07	4 19	2 74	6 94	15 29	32 21	35 96	64 04
3 63	3 51	3 93	4 50	3 92	4 75	19 60	22 75	49 02	50 94
6 30	4 40	5 73	4 54	4 96	4 32	11 86	11 90	56 21	43 75
5 01	6 34	5 34	4 20	5 46	4 10	15 17	11 60	52 42	47 60
2 60		3 35		8 18		70 25		96 05	4 00
5 97	4 19	6 06	4 33	5 87	4 25	17 01	17 05	56 28	43 77
3 93	4 23	4 99	5 24	5 31	5 63	20 40	24 60	47 20	52 84
4 35	2 87	4 56	3 56	5 06	3 57	16 63	16 50	52 77	47 25
	3 97								100 0
	4 0		3 0		1 0				100 0

The latter value has been used in the calculation of the genetic dose However for our investigations the numerical difference between the mean values defined in these two ways turned out to be of no practical importance

The mean values of the gonad doses according to our measurements are recorded in Tables 5 and 6 These give the probable mean gonad dose in mrem per examination for adults and for children below the age of 10 years The foetal gonad dose is taken to be equal to the ovary dos except for pelvimetry and the obstetrical abdomen

Chest heart lung etc All examinations commonly performed in the chest region are taken together The male gonad dose was based on 105 measurements Representative measurements in women have been more difficult to carry out Phantom measurements and estimates indicate that the ovary dose is of the same order of magnitude as the testis dose only a little higher The testis dose in 31 boys was below 1 4 mrem per examination In spite of the high frequency of these examinations the contribution to the genetic dose is relatively low

Chest — mass miniature radiography Only subjects above the age of 10 years are subjected to this kind of examination The testis dose was measured as an

Table 3 *(cont)*

	30—34 years		35—39 years		40—44 years	
	M	F	M	F	M	F
Chest heart lung	2 80	2 05	4 17	3 26	4 86	2 54
Mass chest civil	4 23	4 04	4 58	4 54	4 32	4 30
Mass chest military	9 5	1 2				
Femur	1 96	1 13	2 49	0 90	3 10	1 66
Hip	*1 16*	*0 92*	*1 16*	*1 22*	1 40	2 45
Pelvis	1 75	1 50	3 13	2 50	2 88	2 25
Lumbosacral spine	4 68	3 06	6 89	4 01	6 50	5 10
Urography	3 92	*2 62*	4 74	4 07	4 36	5 26
Urethrocystography	4 09		2 60		1 12	
Stomach	3 79	2 76	4 93	3 44	5 74	3 40
Colon	0 95	2 34	3 10	2 84	3 29	3 60
Abdomen	3 03	*2 8[illegible]*	2 90	3 61	4 06	2 74
Pelvimetry and abd obst		27 45		13 74		7 85
Hysterosalpingography		34 0		27 0		9 0
All other (not dental)						

patients or in the phantom were as follows adult males 759, adult females 316, 'phantom females 115, male children 166 and female children 42 This *makes in all 925 measurements in males and 473 in females, a total of 1 398* gonadal observations

These measurements were undertaken in ten different roentgen departments, in a childrens clinic, and in some smaller establishments Special measurements were carried out in each roentgen department by means of the phantom, in order to assess the ratio ovary dose/rectal dose for each type of examination and for the equipment and technique in use A value in the range 1 0 to 2 0 was generally found These correction factors have been applied to all doses measured in the rectum, in order to find the true ovary dose

Results

The mean gonad dose was calculated for each department for each type of examination and for each sex The mean dose for all the ten departments was then computed *from these values* An example is given in Table 4 which contains data for the examination of the lumbosacral spine The mean gonad dose for all departments is calculated in two ways either directly with regard to the number of departments, or by taking *the relative examination frequency into* account

Table 5

Gonad doses in roentgen diagnostics for males

Type of examination	Probable mean gonad doses in mrem per examination	
	Adults	Children
Chest heart lung	1 1	(1 1)
Chest mass radiography	0 12	(0 12)
Femur	378	(109)
Hip	357	(64)
Pelvis	350	(81)
Lumbosacral spine	121	280
Urography	202	(33)
Urethrocystography	1 930	
Stomach	2 6	63
Colon	172	73
Abdomen	61	

Values in brackets uncertain value for adults used in the calculation of the genetic dose

Table 6

Gonad doses in roentgen diagnostics for females

Type of examination	Probable mean gonad doses in mrem per examination		
	Adults	Children	Foetus
Chest heart lung	2 0	(2 0)	2 0
Chest mass radiography	1 0	(1 0)	1 0
Femur	10	20	10
Hip	148	105	148
Pelvis	126	91	126
Lumbosacral spine	550	230	550
Urography	376	150	376
Stomach	17	93	17
Colon	1 910	(500)	1 910
Abdomen	165		165
Hysterosalpingography	553		
Pelvimetry	est 800		est 900
Obstetrical abdomen	est 400		est 600

Values in brackets uncertain value for adults used in the calculation of the genetic dose est = estimate based on exposure data and skin dose measurement

Table 4

Examination of the lumbosacral spine in adults — Example of calculation of the mean gonad dose

Department	Annual examinations	Per cent	Number of measurements		Mean gonad dose in mrem	
			Males	Females	Males	Females
1	1 605	15.33	16	27	68	660
2	1 152	11.00	2	1	33	412
3	723	6.90	7	12	158	354
4	543	5.19	4	6	47	515
5	820	7.83	9	11	7	204
6	1 650	15.75	4	2	37	691
7	1 150	10.98	9	11	650	605
8	760	7.25	3	6	100	716
9	830	7.93	4	9	70	605
10	1 240	11.83	4	6	33	502
Total	10 473	99.99	62	91		
Mean gonad dose (according to number of departments)					120	529
Mean gonad dose (according to relative exam. frequency)					121	550

average for various groups since the doses were generally too low to be registered for only one single roentgenogram. The highest dose recorded was 0.85 mrem/exposure for a group of eight subjects. The measurements were made with five different radiography units. The mean testis dose was only 0.12 mrem/exp, and from this the ovary dose was estimated not to exceed about 1.0 mrem/exp.

Femur. In most cases, an a.p. projection and a lateral one are obtained (with 18 × 24 cm, 15 × 30 cm and 15 × 40 cm films). If careful shielding is not ensured the testis may easily be exposed to high doses. Shielding was practised in roughly 50 % of the cases in which measurements were made.

Hip. One or both hips may be radiographed so that the number of exposures may range from one to four. Both hips may be taken on one 30 × 40 cm film, or each side examined separately, generally on 18 × 24 cm film. Various a.p. projections are in use. Shielding of the scrotum and ovaries was performed in most of the ten departments, and at the childrens clinic. *With no shielding*, the testis dose in particular rose to high values. The highest testis dose observed was 3 200 mrem in a series of four roentgenograms.

mostly performed in males The gonads fall within the useful beam, and the testis dose may be very high if no shielding is applied Due to the age distribution of the examinations (Table 3) the genetic dose is, however, relatively low

Stomach (barium meal) In the examination of the upper gastro intestinal tract a combination of radiography (with 13×18 cm 18×24 cm and 24×30 cm film) and fluoroscopy is employed An average fluoroscopic time of 3 9 min was recorded for the 76 patients in whom gonad dose measurements were made The gonad dose in adults is low the gonad dose in children being of greater importance In the childrens clinic 25 measurements were made and the gonad doses were significantly higher than for adults

Colon (barium enema) A combination of radiography and fluoroscopy is also used in the examination of the colon or the lower gastro intestinal tract Most of the measurements were carried out in males, namely 54 recordings It is difficult to carry out direct measurements in women and only 15 such measurements were made 10 rectal and 5 vaginal We had to rely mostly on phantom measurements in the case of women One or more colon examinations of the phantom were performed in each department by the radiologist who tried to copy an average colon examination both with respect to the number of roentgenograms usually obtained and the fluoroscopic time Any correction for the possible shadow effects resulting from the contrast material was not included neither for the measurements in the patients nor for those performed in the phantom High ovary doses were uniformly established for this examination The examination usually consisted in obtaining several a p p a and lateral projections on 18×24 cm 24×30 cm and 30×40 cm film The average fluoroscopic time in 71 colon examinations was assessed to 5 5 min In the phantom measurements radiography and fluoroscopy usually gave a contribution of the same order of magnitude to the ovary dose The ovary dose in girls Table 6 was uncertain and the dose for adults was used in the calculation of the genetic dose Shielding of the scrotum was employed in slightly more than half the number of departments engaged

Abdomen The number of roentgenograms obtained of the abdomen are usually between two to five often with a combination of fluorosocopy Commonly the film size is 30×40 cm The ovaries fall to a large extent within the primary roentgen beam

Hysterosalpingography The examination consists generally of four a p and p a projections film size 18×24 cm Some fluoroscopy is usually included the time

Table 7

Estimated gonad doses in pelvimetry

Projection	Dose in mrem to	
	Maternal ovaries	Foetal gonads
Lateral	600	600
Antero posterior	200	300

Pelvis. One 30 × 40 cm a.p. film is obtained. In six of the departments shielding of the scrotum, at least partially, was performed. Shielding of the ovaries is difficult or nearly impossible to achieve. The lowest ovary dose observed was 44 mrem in a department where 120 kV was used for roentgenograms of this kind.

Lumbosacral spine. According to the statistical material collected, the frequency of examinations of the lumbosacral spine was comparatively high. Considerable gonad doses, and in particular ovary doses, have been observed. This examination was in our material found to give the highest contribution to the genetic dose. Two a.p. and two lateral projections covering the lumbal and sacral regions are generally obtained. The lateral projection of the sacral region may easily lead to high ovary doses, and a few departments tried to avoid this projection in young women and girls. Shielding was carried out to some extent. The film size was commonly 18 × 24 cm and 24 × 30 cm (Table 4).

Urography. This examination consists on the average of 2 to 5 a.p. projections, and sometimes one p.a. projection as well, of the abdominal or bladder region. Some additional roentgenograms may be obtained but these are limited to the region of the kidneys and contribute little to the gonad dose. The above mentioned projections of the abdominal and bladder regions determine the radiation load to the gonads. The ovary dose is ordinarily assessed to be around 80 to 150 mrem for each of these projections. The primary radiation field should not include the scrotum but this may easily happen when a proper and accurate limitation of the primary field is lacking. Film size: 18 × 24 cm, 24 × 30 cm and 30 × 40 cm. As in the case of the examinations already dealt with, shielding of the scrotum was only partially performed.

Urethrocystography. The examination may consist of 4 to 6 a.p. or oblique projections on 18 × 24 cm and 24 × 30 cm film. This type of examination is

Table 9

Gonad doses in roentgen therapy for non malignant conditions

Irradiated body region	Exposure to skin in the treatment field	Resulting average gonad dose in mrem	
		Male	Female
Shoulder		15	18
Arm upper		12	30
Arm lower		14	33
Hand		14	30
Cervical spine		7	10
Thoracic spine	100 R	23	47
Lumbosacral spine		510	16 100
Pelvis		690	5 300
Hip		4 220	520
Knee		390	56
Leg		140	47
Foot		94	9

It is evident that the treatment of lumbosacral spine pelvis hip and knee leads to significant gonad exposure

Obstetric abdomen One 30×40 cm a p film is usually obtained and occasionally one lateral or another a p or p a film as well No direct measurements were obtained and we have chosen to use the dose values from two a p projections as given in Table 7 This may mean an overestimation of the dose, particularly in the case of the foetal gonads our estimate of the genetic dose should then be on the safe side

Equipment The equipment at disposal in the departments and installations where the gonad dose measurements were made was of conventional type Image intensifiers were in use in 1959 but did not play such an important part as significantly to affect the genetic dose even to day this seems doubtful

The speed of the film in use was almost exclusively similar to that of Kodak Blue Brand Ilford Red Seal Gevaert Curix Rapid and the intensifying screens were generally of the medium speed (universal) type High voltage technique was only partially in use One of the departments however tried to use 120 kV for most of the examinations for which the ovaries are in the useful beam thus achieving a reduction of the ovary dose to a value around one half of that resulting from the conventional low voltage technique

Table 8

Genetic dose in roentgen diagnostics in Norway 1958—1959

Type of examination	Annual genetic dose in mrem per person				Per cent
	Male	Female	Foetus	Total	
Chest, heart, lung	0.05	0.07		0.12	1.3
Chest mass radiography	0.02	0.06		0.08	0.9
Femur	0.54	0.01		0.55	5.8
Hip	0.57	0.19		0.76	8.0
Pelvis	0.86	0.27	0.01	1.14	12.1
Lumbosacral spine	0.73	1.69	0.11	2.53	26.8
Urography	0.34	0.48	0.03	0.85	9.0
Urethrocystography	0.10			0.10	1.1
Stomach	0.05	0.07		0.12	1.3
Colon	0.15	1.11	0.08	1.34	14.2
Abdomen	0.11	0.25	0.01	0.37	3.9
Hysterosalpingography		0.10		0.10	1.1
Pelvimetry		0.19	0.50	0.69	7.3
Obstetrical abdomen		0.10	0.34	0.44	4.7
All other examinations	0.11	0.12	0.01	0.24	2.5
Total	3.63	4.71	1.09	9.43	100.0

being around a minute. The ovary dose was measured in a few patients, and in addition by means of the phantom. The ovary dose is high but the frequency of examinations is low.

Pelvimetry. Apparently, only about 900 such examinations were performed in 1958. Very few patients were thus available during the period for which measurements were made in each department, and rectal measurements were withheld in these patients. Exposure techniques and exposure data were analysed, and some skin dose measurements were made. From this material an estimate of the ovary dose was made. The distances to the maternal ovaries and to the gonads of the foetus for various projections were taken from a paper by CLAYTON, FARMER & WARRICK (1957).

Pelvimetry is generally based on a combination of one lateral and one a.p. projection. For a.p. projections in the semi-erect position the ovary dose may be higher than indicated in Table 3. The dose given to the foetal gonads is based on the assumption of no shielding. It would thus appear that an average pelvimetry should produce mean ovary and foetal gonad doses of some 800 mrem and 900 mrem, respectively.

Table 10 *(cont)*

40—44 years		45—49 years		50—54 years		55—59 years		> 60 years	
M	F	M	F	M	F	M	F	M	F
23 590	27 670	21 100	27 100	42 860	49 240	48 970	47 650	141 730	102 680
4 800	5 100	428	6 900	4 350	578	6 900	498	4 565	498
1 570	5 6 0	3 200		4 030	3 200	1 628	5 700	8 500	1 800
	8 275	20 800	4 650	3 300	5 200	14 670	5 000	16 770	14 640
9 815	16 798	13 870	21 330	47 615	43 510	49 730	35 680	120 200	140 400
2 600	1 200	498	1 800	17 915	5 300	5 400	10 400	11 998	15 470
16 800	1 298	12 815	16 160	30 700	14 470	49 078	30 370	92 660	97 220
								7 000	4 900
2 740		2 000	5 740	3 600	12 800	7 070	4 520	42 790	81 720
3 470	6 470	2 140	15 160	18 400	18 215	13 615	33 600	100 580	164 520
			1 800	1 070	1 800		1 070		1 400
600	4 370	430	1 800	460	6 830	8 015	4 470	17 315	25 430

according to Table 8 a value of some 10 mrem/person and year It may be difficult to indicate exactly the accuracy of this estimate but it seems highly improbable that the genetic dose exceeds a value twice that given in Table 8 The error in the estimate is probably not greater than about 30 %

The value found for the genetic dose is of the same order of magnitude as reported from many other countries LARSSON (1957) reported an annual genetic dose in Sweden of 37 8 mR/person and similarly HAMMER JACOBSEN (1963) found 21 6 mR/person for Denmark The annual genetic dose in England and Scotland amounts to 14 1 mR/person according to the second report from the Adrian Committee (1960) SEELENTAG et coll (1960) assessed the annual genetic dose to 14 mR/person for the population of South Bavaria

As is evident from Table 8 only relatively few types of examinations are responsible for the major part of the genetic dose The examinations femur hip pelvis lumbosacral spine urography colon and the obstetric examinations thus contribute 88 % to the total genetic dose

Dental radiography has not been explicitly mentioned in the tables In ten different dental clinics film measurements were made for 1 201 exposures in 281 patients (not included in Table 5) The mean testis dose was 0 21 mrem/ exp The ovary dose could not be directly measured but only the dose to the skin above the ovaries This dose was assessed to 0 34 mrem/exp which probably corresponds to an ovary dose of around 0 1 mrem/exp These

Table 10

Total annual exposure dose to skin in six average departments by age and sex in Norway during 1963

Irradiated region	25—29 years		30—34 years		35—39 years	
	M	F	M	F	M	F
Shoulder		2 600	9 340	515	2 915	8 785
Arm upper						
Arm lower			1 800	900		1 200
Hand					400	1 200
Cervical spine			1 070	1 800	5 828	18 698
Thoracic spine						
Lumbosacral spine	1 200				3 600	800
Pelvis			690			
Hip						
Knee	2 100			600		1 070
Leg	800					
Foot		1 500	1 670	1 070	2 400	900

Shielding of the gonads was carried out routinely at some department, but not all. For examinations that may easily result in high testis doses, roughly around 50 % of the men were shielded.

Genetic dose. The genetic dose was calculated by means of the previously given formula, and the data are shown in Table 8. As to the methods applied in the calculation, a few comments should be made. In examinations for which the gonad dose in children is uncertain, the value for adults was used in the calculations. The dose to children is, or may be expected to be, lower than for adults. This method should then lead to an overestimation of the genetic dose rather than the opposite.

The assessment of the genetic dose due to irradiation of the foetus has been based on the following facts and assumptions. The birth frequency for women of fertile age is 7.76 % per year. Thus the probability of a woman of fertile age being pregnant is 9/12 · 7.76 = 5.83 %. For women undergoing roentgen examination it seems reasonable to use a lower value. We have chosen to apply a third of this value, i.e. 1.95 %. The value 2.7 is used as an approximation for the child expectancy factor of the foetus (see Table 1). The calculation is different for obstetric examinations since the pregnancy is an established fact.

The estimate of the genetic dose in roentgen diagnosis in Norway reaches,

Table 12

Total genetic dose in radiation therapy in Norway during 1963

Category of treatment	Annual genetic dose in mrem per person
Treatment of non malignant conditions	0 6
Treatment of malignant conditions	0 1
Grenz ray and contact therapy	0
High energy therapy	0
Errors	±0 3
Total genetic dose in therapy	0 7±0 3

received by a patient of either sex The gross skin doses and their distribution over age groups and sexes have been sorted out by means of punch cards onto which patient information received from six representative roentgen departments was fed On this basis a survey chart given in Table 10 could thus be built up It is evident that the highest skin doses are applied to four body regions namely the shoulder the cervical spine the lumbosacral spine and the knee The simple reason for this is the frequency of treatment of these four regions

The final information required was the total number of sessions (single treatments) that had been given to the twelve selected body regions in the course of one year This information was collected from 42 departments i e 50 % of Norway s 84 roentgen therapy centres The year selected was 1963 The distribution of total sessions to the body regions is evident from Table 11

The last three columns of Table 11 give the resulting annual genetic doses computed relative to the region treated and to sex The resulting figure of 0 6 mrem is low thanks to careful aiming of the radiation field and good coverage of the patient With a less satisfactory technique it is estimated that the genetic dose might easily be three to four times higher It will be noted that the treatment of the lumbosacral spine contributes 50 % to the genetic dose and the treatment of men s knees 25 % Good coverage is therefore of special importance in these instances

It has not proved necessary to collect much material on the treatment of malignant conditions because it is obvious that the vast majority of these patients falls into age groups for which the child expectancy factor rapidly approaches zero with malignant cases included the total genetic dose will increase by no more than 0 1 mrem

The possible contribution to the genetic dose from grenz ray therapy and contact therapy has also been evaluated The gross skin doses are not great

Table 11

Genetic dose in roentgen therapy for non-malignant conditions in Norway during 1963

Irradiated body region	Number of seances in 42 roentgen departments in 1963		Annual genetic dose in mrem per individual		
	M	F	M	F	M + F
Shoulder	20 680	20 994	0.0106	0.0078	0.0184
Arm, upper	2 651	1 858	0.0012	0.0020	0.0032
Arm, lower	1 295	1 362	0.0005	0.0008	0.0013
Hand	1 212	2 187	0.0009	0.0011	0.0020
Cervical spine	13 578	14 474	0.0026	0.0009	0.0035
Thoracic spine	1 235	1 676	0.0008	0.0002	0.0010
Lumbosacral spine	9 589	14 830	0.1660	0.1580	0.3240
Pelvis	3 071	4 534	0.0785	0.0000	0.0785
Hip	1 051	1 795	*0.0022*	*0.0087*	*0.0109*
Knee	10 260	19 533	0.1360	0.0039	0.1399
Leg	318	247	0.0108	0.0001	0.0109
Foot	2 648	4 021	0.0016	0.0012	0.0028
			0.4117	*0.1847*	*0.5964*
			Total 1963 ~ 0.6 mrem		

measurements refer to adults, and for children the doses may be somewhat higher. With these gonad doses, dental radiography obviously cannot contribute significantly to the genetic dose.

Radiation therapy

The genetic dose from radiation therapy may be evaluated by the same formula as previously mentioned but the pertinent statistical data, going into the formula, had again to be specially collected from institutes of radiology.

Starting with the treatment of non-malignant conditions, twelve different body regions to be subjected to therapy were selected. The actual measurements of the gonadal doses following the treatment series were carried out in six different institutes of radiology, and the objects of treatment was the above-mentioned phantom. The phantom in all the institutes was treated as far as possible as a living patient would be, and care was taken not to intervene in the local treatment techniques.

The results are listed in Table 9, which serves as a key allowing a general extrapolation from gross skin exposure (100 R) to the gonad doses in mrem

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Errors	±0 3
Total genetic dose in therapy	*0 7±0 3*

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It has not proved necessary to collect much material on the treatment of malignant conditions because it is obvious that the vast majority of these patients falls into age groups for which the child expectancy factor rapidly approaches zero with malignant cases included the total genetic dose will increase by no more than 0 1 mrem

The possible contribution to the genetic dose from grenz ray therapy and contact therapy has also been evaluated The gross skin doses are not great

and the gonad doses resulting from the skin irradiation are so small that this special treatment with soft radiation will not have significant influence upon the genetic dose.

Preliminary investigations of the treatment with high energy equipment like cobolt 60 units and betatrons have been carried out. This treatment is in Norway applied exclusively to malignant conditions, in which, as stated above, the child expectancy factor rapidly approaches zero and leads to negligible genetic irradiation. The skin dose to gonad dose relationship for 31 MV roentgen rays from a betatron has been investigated to some extent and found to be of the same order of magnitude as for conventional roentgen rays, only some 30 % more favourable. The reason is that the radiation scattered inside the body follows the direction of the hard primary beam more closely.

It did not appear that the radioactivity induced in the body by the 31 MV roentgen rays could affect the gonad doses and in this way have any genetic importance.

The present investigation which has been based on information from many different sources must contain some errors. The greatest inaccuracy most likely lies in gonad doses assumed from the skin dose, because the treatment technique varies considerably from institute to institute. The total error in the investigation is estimated to be $\pm$ 0.3 mrem.

The total genetic dose following radiation therapy is given in Table 12.

SUMMARY

The gonad doses resulting from diagnostic and therapeutic roentgen procedures in Norway during the period 1959—1964 were surveyed. Measurements were undertaken in ten roentgendiagnostic departments, six therapy departments, in a childrens clinic and in some smaller establishments. Examinations of the femur, hip, pelvis, lumbosacral spine and the lower gastro-intestinal tract, as well as urologic and obstetric examinations, contributed almost 90 % of the total diagnostic genetic dose. Treatments of the lumbosacral spine and men's knees contributed with 50 % and 25 %, respectively, to the total therapeutic genetic dose.

ZUSAMMENFASSUNG

Für die Periode 1959—1964 wurde die Gonadendosis ausgearbeitet, die alle Patienten in Norwegen durch röntgendiagnostische oder röntgentherapeutische Massnahmen erhielten. Die Messungen fanden in zehn röntgendiagnostischen und in sechs therapeutischen Abteilungen, in einer Kinderklinik und in einer Anzahl kleinerer Abteilungen statt. Untersuchungen des Oberschenkels, der Hüftgelenke, des Beckens, der lumbosakralen Wirbelsäule, des unteren Darmabschnittes und urologische und gynäkologische Untersuchungen waren für 90 % der gesamten diagnostisch genetischen Dosis verantwortlich. Bei Bestrahlung der lumbosakralen Wirbelsäule und des Knies an Männern war der Beitrag zu der therapeutisch genetischen Dosis bezw. 50 % und 25 %.

RÉSUMÉ

Les auteurs ont calculé les doses aux gonades provenant des examens et des traitements par les rayons de roentgen au cours de la période 1959—1964 en Norvège Des mesures ont été faites dans 10 services de radiodiagnostic 6 services de radiothérapie dans un service pédiatrique et dans plusieurs autres petits établissements Les examens du fémur de la hanche du bassin de la colonne lombo-sacrée et de la partie inférieure du tube digestif ainsi que les examens urologiques et obstétricaux donnent près de 90 pour cent de la dose génétique totale due au diagnostic Le traitement du rachis lombo-sacré et des genoux chez l homme donnent respectivement 50 et 25 de la dose génétique totale d origine thérapeutique

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INFLUENCE OF COLLIMATING SYSTEMS ON DOSE DISTRIBUTION FROM 10 TO 35 MeV ELECTRON RADIATION

by

H SVENSSON and G HETTINGER

Tubes are often used for collimation and definition of the radiation field in therapy with high energy electrons The dose distribution in the patient is however strongly influenced by the kind of field applicators used Electrons scattered from the walls of the tube may increase the dose at small depths, which results in an increased skin dose (MARKUS 1960, LOEVINGER et coll 1961) More electrons are scattered from the tube walls to the vicinity of the field edges than to the field centre which apparently improves the isodose picture (v d DECKEN et coll 1956 BRADSHAW & MAYSENT 1964, BATCHELOR et coll 1959)

A modified collimating system, mainly consisting of a brass field applicator placed close to the skin, will be described in the present paper The dose distribution obtained with this collimating system is compared with that obtained with the original tube collimator for a Brown Boveri Asklepitron unit

Description of the collimating systems The original collimator consists of a perspex tube connected to the so called sandwich, a metal plate containing

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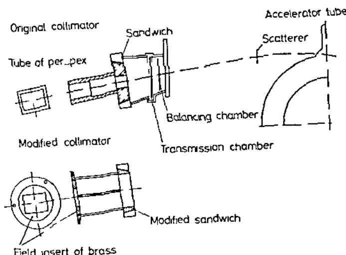


Fig 1 The collimating system of a Brown Boveri Asklepitron is shown to the left at top of figure the original tube being of perspex The modified collimator with a field insert of brass is shown below

layers of aluminium iron and lead The gradient of the tube walls and the hole in the sandwich are matched to a focus of 110 cm from the patient (Fig 1)

The modified collimator consists of a brass plate of 13 mm thickness and 22 cm or 18 cm diameter this plate is placed close to the patient The hole in the modified sandwich is at least of the same size as that in the brass plate The latter can be supplied with several field insets defining the field sizes (Fig 1)

Dose rate The electrons on their way from the accelerating tube to the patient pass through a scatterer consisting of 0 3 or 0 4 mm copper a transmission chamber (WIDEROE 1959) and a balancing chamber (PETTERSSON & HETTINGER 1965) A broad angular distribution of electrons is obtained through scattering processes When the original collimator is used and the field size is small only those electrons that have been scattered through small angles from the central ray reach the patient All other electrons are absorbed by the sandwich This is one of the reasons for obtaining lower dose rates with a field of small size than with a field of larger size Especially at low primary electron energies where the cross sections for scattering processes are high the dependence of dose rate on field size is marked The variation of dose rate with field size at 13 MeV electron radiation is shown

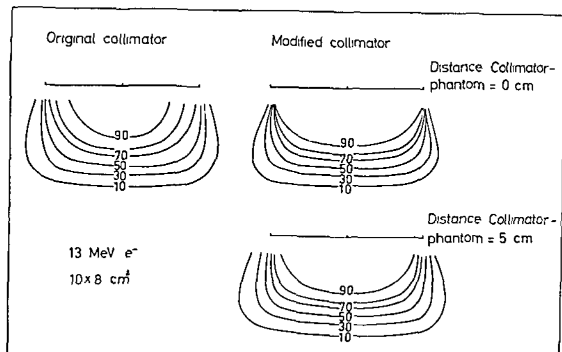


Fig 4 Isodose curves obtained with different collimating systems for 8 cm × 10 cm field size and 13 MeV electron radiation

collimator, at a distance of 5 cm between collimator and phantom, is shown *in the lower curve of Fig 4*

Discussion

It was found that if the field limitation for the electron beam is achieved with a metal collimator close to the patient s skin, the dose picture is improved The dose rate, in comparison with the original collimator, is increased, better *isodose curves are obtained, and the skin dose situation is improved* The ease with which switching over from one field to another can be made constitutes a further advantage when using the modified collimator, only a small *field inset has to be changed The calibration factor of the betatron monitor* also shows less dependence on field size

The dimension of the brass plate is about twice that of its hole which causes some practical difficulties when the surface of the region to be irradiated is irregular, as for instance in cases of head and neck tumours The influence on the isodose curve of a 5 cm gap between brass plate and phantom surface may be observed from the lower curve in Fig 4 Still, the isodose curve is somewhat better than that obtained with the original collimator placed close to the phantom, as may be seen from the upper curve in Fig 4

SUMMARY

The influence of the collimating system on the dose distribution from 10—35 MeV electron radiation was studied A brass collimator placed on the skin gave better isodose curves and less contribution from low-energy scattered electrons e g a better skin sparing effect in comparison with the original perspex tube The modified collimator increases the output of the betatron

ZUSAMMENFASSUNG

Der effekt des Kollimatorensystems auf die Dosisverteilung bei 10—35 MeV Elektronenstrahlung wurde studiert Beim Anbringen von einem Messingkollimator auf die Haut wurden bessere Isodosiskurven und einen verminderten Beitrag von Streuelektronen erreicht d h der hautsparenden Effekt war grösser als beim gewohnlichen Perspextubus Mit dem modifizierten Messingtubus wurde die Ausbeute des Betatrons erhohert

RÉSUMÉ

Les auteurs ont étudié l influence du système de collimation sur la distribution de doses dans l irradiation par des électrons de 10 à 35 MeV Un collimateur en laiton placé sur la peau donne de meilleures courbes isodoses et une moindre contribution d électrons diffusés de faible énergie c est à dire ménage mieux la peau que le tube d origine en perspex Ce collimateur modifié multiplie environ par deux le débit du bétatron

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CHROMOSOME ANALYSIS OF AN INFANT AFTER INTRAUTERINE IRRADIATION

by

MARIA KUCEROVA

An opportunity arose of making a chromosome analysis of an infant subjected to intrauterine irradiation with a large roentgen dose during the treatment of the mother for carcinoma of the uterine cervix.

The mother of the child, 36 years old at the time of delivery, had received a dose of 14 350 R to the uterine cervix in 26 separate applications during the fifth and sixth months of gestation. Factors: 180 kV, 10 mA, filter 1 mm Cu. Caesarean section was performed at about the 32nd week, the weight of the infant on birth was 1 980 g, and the body length was 44 cm. No malformation was evident.

Chromosome analysis of the peripheral leukocytes of the child was performed *12 months postnatally, i. e. 14 months after the last irradiation.* Chromosome analysis of the mother was carried out 15 months after irradiation, also with the peripheral leukocytes. The technique roughly followed that of MOORHEAD et coll. (1960). *Three day cultivation of stimulated PHA gave a sufficient number* of evaluable mitoses; after staining with Giemsa solution the workable metaphases were photographed and analysed. The mitoses were classified according to the chromosome number into modal and non modal, and according to the shape and arrangement of chromosomes into normal and aberrant.

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Table

The effect of intrauterine irradiation — Chromosome analysis of peripheral leukocytes of child as compared to mother and normal controls

	< 46	46	46 <	Number of analysed metaphases	Number of aberrant mitoses		Per cent aberrant mitoses	Polyploid
					Total	Simple complex pseudodipl		
Child	19	173	4	196	13	3 6 4	6 63	25
Mother	13	67	3	83	5	1 2 2	6 0	5
Control	75	519	54	648	5	2 0 3	0 77	5

Aberrations were classified in three groups

1 *Simple* Direct consequences of simple breaks (fragments difragments chromatid and isochromatid breaks and gaps deletions)

2 *Complex* Consequences of multiple breaks and rejointings (dicenters abnormal chromosomes and/or ring chromosomes)

3 *Pseudodiploid mitoses* Mitoses with a normal number and shape of chromosomes but with incorrect distribution into groups according to the Denver nomenclature

Chromosome analyses of the peripheral leukocytes of seven healthy women irradiated with a single diagnostic dose were used as controls The results are given in the accompanying Table

In evaluating the results consideration must be given to the fact that the exact dose received by the child is unknown since the air dose of 14 350 R was directed towards the uterine cervix of the mother The true dose received by the foetus was in all probability essentially lower It is also not clear to what degree the chromosomal analysis 14 months after irradiation indicates the changes induced A portion of the aberrant cells might already have been excluded from further cell division while other cells need not necessarily have recovered as to be capable of entering mitosis so that their production by irradiation could have been detected

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The results, especially in the child, are hardly comparable with the data in the literature, which concern mostly adult subjects and comprise a number of variables such as the dose and type of radiation, mode of administration, extent of the irradiated region and the time that elapsed between the last irradiation and the chromosomal analysis With this variability of conditions the stated percentage of aberrant mitoses varied as follows 16 4 to 32 1 % (BUCKTON et coll 1962), 29 % (LINDGREN & NORRYD 1962), 2 to 20 % (BENDER & GOOCH 1962), 14 to 23 % (BENDER & GOOCH 1963), 1 to 42 % (SASAKI et coll 1963), and 1 4 to 6 1 % (DOIDA et coll 1965)

The frequency of aberrant mitoses in the present cases (i e 6 %) is significantly higher (counted by the test of difference of two binominal distributions) than in the controls and falls into the range which according to the literature is *characteristic of irradiated rather than normal subjects* The number of polyploid cells was clearly higher in the child It is interesting that the chromosomal analysis of cells of the mother and child revealed a similar frequency of aberrations in spite of the fact that their irradiation was hardly comparable

SUMMARY

Intrauterine irradiation in the fifth and sixth months of pregnancy induced a highly significant increase in the percentage of aberrant mitoses in the peripheral leukocytes of the infant as detected 14 months later The percentage of aberrant mitoses in the mother 15 months after the irradiation was nearly the same as in the child

ZUSAMMENFASSUNG

Vierzehn Monate nach intra uteriner Bestrahlung im funften und sechsten Schwangerschafts monat wurde eine bedeutsame prozentuale Steigerung der Mitosen in den Leukozyten der peripheren Zirkulation bei dem Saüglinge gefunden Der prozentuale Anteil von abnormen Mitosen war nach 15 Monaten ebenso gross bei der Mutter wie bei dem Kinde

RÉSUMÉ

L irradiation intra utérine aux 5ème et 6ème mois de la grossesse provoque une augmentation très significative du pourcentage des mitoses aberrantes dans les leucocytes du sang *périphérique* de l enfant examiné 14 mois plus tard Le pourcentage des mitoses aberrantes chez la mère 15 mois après l irradiation est a peu près le même que chez l enfant

Rate of substitution

In the opinion of the Panel the slow pace at which radium substitutes are being adopted is a function of the conservatism of long established radiotherapy departments and the caution of newly founded institutes The advanced institute usually has a large and satisfactory stock of radium which it employs in well tried techniques that yield good results It has no incentive to adopt new materials or techniques that appear to offer few if any advantages The developing institute on the other hand is loath to plunge into new methods which are not backed by a large body of clinical experience However there is now sufficient evidence to state that there is no difference between the clinical effects of radium and its substitutes (excluding low energy γ emitters) so that established techniques may be carried over with confidence from one to the other

Furthermore while the relative merits of radium and its substitutes can still be argued for conventional applications using rigid sources there is no doubt that many useful new techniques can be developed using thin flexible sources For these applications ^{192}Ir is recommended

Afterloading

Afterloading techniques are those in which guides are initially placed in the patient and the radioactive sources intoduced later into the guides under more favourable conditions of protection The guides may be for example stainless steel or nylon tubes or more elaborate applicators for intracavitary therapy If the sources are introduced manually the technique may be termed simple afterloading On the other hand machines are currently under development in several countries whereby the sources are introduced and withdrawn by remote control Such machines will virtually eliminate the hazard to personnel and place intracavitary therapy on a par with teletherapy

The Panel considered that simple afterloading techniques have now reached the stage when they can be recommended even to less advanced institutes These techniques offer important advantages relative to conventional preloading methods in terms of the accuracy of placing the sources and the radiation protection of personnel However there is an urgent need for the commercial production of simple afterloading applicators for intracavitary therapy of gynaecological tumours

Remote controlled afterloading machines cannot yet be recommended to all institutes There are several problems of a technical clinical and radiobiological nature In particular the use of high activity sources (i e a few curies) in these machines will reduce the exposure time to minutes and enable patients to be treated on an outpatient basis However such irradiations introduce difficult questions relating for example to dose rate and fractionation When these remaining problems have been solved remote afterloading machines are likely to be widely used Meanwhile the Panel urges advanced radiotherapy centres to assist in the development and trial of this type of equipment

RECOMMENDATIONS ON SOURCES AND TECHNIQUES

1 *For temporary applications* by preloading techniques ^{137}Cs sources are recommended if a new stock is to be acquired Continued use of existing double-encapsulated radium sources of modern construction is acceptable Also ^{60}Co and ^{192}Ir sources may be considered if they can be produced cheaply in an available reactor

SMALL SEALED SOURCES IN RADIOTHERAPY

Report on IAEA Panel (Summary of Proceedings June 1966)

In 1964—1965 the International Atomic Energy Agency carried out a survey of the stocks of small sealed radiation sources and their applications in surface, intracavitary and interstitial therapy. These types of therapy will be collectively referred to below as brachytherapy. The survey was made in Canada, France, Scandinavia, the U.K. and in a group of Middle Eastern countries. The results showed that in all these countries brachytherapy is to a very large extent synonymous with intracavitary therapy of gynaecological tumours. The volume of other types of work, such as interstitial implants, has decreased in recent years but is now tending to stabilize at a low but by no means negligible level. The replacement or supplementation of radium and radon by sources containing artificial radioisotopes is proceeding very slowly and (except in the case of ^{198}Au grains) has so far taken place in only a small minority of hospitals in any country. *In developing countries brachytherapy remains at a low level in relation to the needs.*

It was against this background that the IAEA convened an international panel to consider the physical aspects of brachytherapy using γ ray emitters. The Panel, which met in Vienna from June 20—24, 1966, comprised 6 radiation physicists, 4 radiotherapists and 5 representatives of manufacturers of radiation sources from 8 countries. In addition, 6 observers attended the meeting, two of them representing the World Health Organization.

Need of a radium substitute

The Panel considered that the main hazard in the use of radium sources lies not in the possibility of explosion through build up of internal gas pressure but in the small but finite possibility of damaging sources during use. The hazard in the event of breakage of a radium source is very great. On this ground alone the Panel felt itself justified in recommending sources of ^{137}Cs, which is now available in insoluble form. In addition, the lower γ ray energy of this isotope permits easier shielding, both external and within body cavities. Finally, the capital expenditure in acquiring a stock of caesium sources is considerably lower than for equivalent radium sources (*approximately one half*), although the total expenditure over several decades may not be very different. These advantages of ^{137}Cs are felt to outweigh the disadvantage of a decrease in source activity of about 2 % per year.

ACTA RADIOLOGICA

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EFFECT OF CYCLOPHOSPHAMIDE ON PAIN IN ADVANCED CARCINOMA OF THE CERVIX

by

NINA EINHORN

Pain is common in advanced carcinoma of the cervix and presents a difficult therapeutic problem whether the lesion is recurrent or metastatic The object of the present investigation was to study the effect of systemic administration of cyclophosphamide on pain of this kind

Material The material consisted of 23 patients with advanced carcinoma of the cervix who had had pain and to whom at least 2 000 mg of cyclophosphamide had been given during one month All the patients had recurrences after intracavitary and external irradiation and the condition was so advanced that curative treatment was considered futile Two of the patients had distant metastases as well as pelvic involvement

The patients were divided into two groups according to whether or not they had experienced a marked alleviation of pain on administration of cyclophosphamide The two groups were compared with respect to the dose of cyclophosphamide the depression of white cells and thrombocytes age and any undesirable side effect such as alopecia and malaise

From the Department of Gynaecology (Director H L Kottmeier) Radiumhemmet Stockholm Sweden Submitted for publication 12 September 1966

2 As an absolute minimum but not necessarily ideal stock ten ^{137}Cs tubes of 20 mm overall length 2 65 mm diameter, 13 5 mm active length and 10 mg radium equivalent are suggested plus twelve ^{137}Cs needles of 42 mm overall length 1 65 mm diameter 30 mm active length and 1 mg radium equivalent These sources should be made available by manufacturers as packs and may be supplemented by packs of sources of other activities

3 *Afterloading applicators* should be used as much as possible and for intracavitary work they should accept the same sources as used for preloaded applicators For afterloading of temporary implants platinum clad ^{19} Ir wire of 0 3 mm outside diameter is recommended Remote afterloading machines are expected to be widely used after further development and trial

4 *For permanent interstitial implants* platinum clad ^{198}Au grains are recommended Radon seeds are equally satisfactory medically where existing plants with trained personnel are available It is desirable to develop inexpensive seeds of low energy emitters preferably with half lives somewhat longer than that of ^{198}Au

Dosimetry

The Panel considered the practical aspects of dosimetry in brachytherapy and made a number of recommendations They included a recommendation to IAEA to proceed with the complication of a brachytherapy atlas i e an atlas of dose distributions for various arrays of sources both for perfect and imperfect geometry The outline of such an atlas has already been formulated It is not intended as a cook book but as a guide to practical therapy with special emphasis on the effect of errors in placing the sources Arrangements will be made to compute the distributions and it is hoped to publish the volume within two years

Other recommendations

The Panel also made recommendations on many aspects of the storage handling and maintenance of sealed sources and on protection A full report of the Panel will be published by the IAEA and will include a selected bibliography Copies of the international survey mentioned at the beginning of this report are available from IAEA

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significant however There were patients with fewer than 1 000 white cells who had no relief of pain and others with a count exceeding 3 000 at the time of subjective improvement

Discussion

Palliation has been reported occasionally in patients with advanced carcinoma of the cervix following the systemic administration of various chemotherapeutic agents (BATEMAN 1958 SELIEI & ECKHARDT 1958 SHIDER et coll 1960 SAMUELS & HOVE 1961) MASTERSON & NELSON (1965) reported signs of regression in 8 to 15 per cent of 52 such patients with systemic administration of various chemotherapeutic agents According to other authors, squamous cell carcinoma of the cervix is notoriously unresponsive to all such agents (RICHARDSON et coll 1962) The conclusions will depend not only on series and methods of treatment but also to a large extent on the criteria used in the evaluation of the palliative effect No evidence has been presented that chemotherapy increases the life expectancy of patients with advanced gynaecologic carcinoma (FRICK et coll 1965)

In a recently presented series of 42 patients with advanced carcinoma of the cervix in which cyclophosphamide treatment was consistently administered *SOLIDORO et coll* (1966) had used the depression of the white cell count in peripheral blood as a guide to the dose These patients *received an average* cumulative dose of 4 900 mg of cyclophosphamide in a mean period of 24 5 days followed by a smaller maintenance dose An objective *regression* was noted in 11 patients (26 per cent) Similar results have been reported by DVORAK *et coll* (1965)

Striking relief of pain obtained by regional chemotherapy in advanced cervical carcinoma has been observed by PARKER & SHINGLETON (1962) and CAVANAGH et coll (1965) The former authors ascribe this relief to a toxic effect of the drug on the nerve fibres of the tissue as well as to arteriolar damage

By the systemic administration of cyclophosphamide in the present series a marked alleviation of pain was achieved in about half the number of patients treated To obtain this relief it was usually necessary to administer toxic doses which resulted in a marked reduction in the white cell and thrombocyte counts

SUMMARY

Twenty three patients with pain from advanced carcinoma of the cervix were treated by systemic administration of cyclophosphamide Thirteen experienced marked relief The effect of the treatment was more closely correlated to depression of the white cell and thrombocyte counts than to the dose

Table

Results of systemic administration of cyclophosphamide for relief of pain in advanced carcinoma of the cervix

	Number of patients	Mean age	Simultaneous radio therapy	Greatest monthly dose mg	Lowest blood counts (mean)		Side effects	
					White cells	Thrombocytes	Alopecia	Malaise
Improved	13	50	2	4 100 mg	2 290	163 000	2	2
Not improved	10	53	2	4 000 mg	2 940	219 000	4	2

Methods Cyclophosphamide was administered intravenously in a daily dose of 200 to 600 mg The maximum dose of 600 mg was given to 14 patients for 5 to 7 days When the planned total amount had been administered, a lower daily maintenance dose was usually given orally provided that this was not contra indicated by the blood cell counts The largest dose received by the patient during a 30 day period was used as a comparable measure

For an evaluation of the alleviation of pain it is necessary to rely on the patient, though the consumption of analgesics may also provide a guide In this series, an improvement was recorded when there was markedly less pain, while patients with slight or uncertain changes were considered unimproved

The depression of white cells and thrombocytes was represented by the lowest value recorded

'Simultaneous radiotherapy' was taken to include treatment given within a month prior to the administration of cyclophosphamide

Results

Thirteen out of the 23 patients treated experienced distinct alleviation of pain in connection with the cyclophosphamide treatment and ten reported no definite relief The improved and unimproved groups differed negligibly with respect to the dose of cyclophosphamide administered the former receiving on an average 4 100 mg and the latter 4 000 mg as the largest monthly amount (see Table) There would, on the other hand seem to be some difference between the two groups with respect to the lowest white cell count with 2 290 and 2 940 cells per mm^3, respectively A difference with respect to the lowest thrombocyte count was also noted These differences were not statistically

significant however There were patients with fewer than 1 000 white cells who had no relief of pain and others with a count exceeding 3 000 at the time of subjective improvement

Discussion

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SUMMARY

Twenty three patients with pain from advanced carcinoma of the cervix were treated by systemic administration of cyclophosphamide Thirteen experienced marked relief The effect of the treatment was more closely correlated to depression of the white cell and thrombocyte counts than to the dose

ZUSAMMENFASSUNG

In 23 Patienten mit vorgeschrittenem Cervix Karzinom wurde Cyclophosphamid systemisch verabreicht und in dreizehn von ihnen wurde Schmerzlinderung erreicht Der Effekt der Behandlung stand in naherem Verhaltnis zur Abnahme der Leukozyten und Thrombozytenzahl als zur Dosis

RÉSUMÉ

Les douleurs dues à un cancer avancé du col de l utérus ont été traitées chez vingt trois malades par l administration de cyclophosphamide Treize malades ont été notablement soulagées L effet de ce traitement est lié plus étroitement à la baisse du nombre des leucocytes et des thrombocytes qu à la dose

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TREATMENT OF NEUROBLASTOMA

by

JAKOB VISFELDT

Neuroblastomas account for 7 % to 10 % of all malignant conditions in children apart from leucaemias and have probably been more intensively studied in recent years than any other tumour affecting this age group Investigation of the tumour as regards biochemistry variable histologic aspects tendency to spontaneous regression and characteristic ability to become benign have led to its more certain diagnosis better assessment of the results of treatment and a more accurate prognosis Those workers who have employed various methods of treatment have in recent years produced not only encouraging results but information that has extended the indications for active therapy

Some of the principles of treatment of this condition are presented in this paper based upon a series of cases treated

Material This consists of all cases of neuroblastoma admitted to our Centre during the 5 year period 1961—1965 This series probably represents about 25 % of all case that had actually occurred in Denmark during this period (see Table)

Case reports

Case 1 A boy born in February 1960 was admitted to hospital in March 1961 with otitis media and upper respiratory infection Explorative laparotomy took place 5 weeks later following the finding of a mass in the left hypochondrium A large tumour arising from the

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Table

Cases of neuroblastoma admitted to the Radium Centre during 1961—1965

Case numbers and sex	Age on onset of symptoms	Presenting symptoms and signs	Age on treatment	Primary site	Metastases
1 ♂	12 months	Catarrhalia otitis media	14 1/2 months	Left retro peritoneal	Pancreas lymph nodes
2 ♂	6 months	Extravasation of blood around eyes temporal swellings	8 months	Right retro peritoneal	Skull mandible
3 ♀	8 months	Nodule in left axilla	9 months	Posterior mediastinum	Costae left axilla
4 ♀	11 months	Fever	12 months	Probably posterior mediastinum	Thoracic spinal canal
5 ♂	6 years	Anorexia fever	6 years 3 months	Left adrenal	Neck left supraclav
6 ♂	13 years	Lumbar pain	13 years 2 months	Probably posterior mediastinum	Thoracic spinal canal corpora
7 ♂	5 years	Sickness fatigue fever	[illegible] years 2 months	Left adrenal	Spleen lymph nodes
8 ♀	2 years 10 months	Fatigue back pain	3 years	Left retro peritoneal	Bone marrow
9 ♀	2 months	Failure to thrive paralysis of legs	5 months	Probably left retroperitoneal	Posterior mediastinum muscles spinal canal

region of the left kidney was invading neighbouring structures superiorly posteriorly and medially Extension into the pancreas was also probable and the para aortic lymph nodes were considerably enlarged The tumour was considered inoperable the histologic examination suggested a neuroblastoma The cells were highly anaplastic

The patient was treated at our Centre with conventional radiotherapy (250 kV) to opposing fields with a total tumour dose of 3 238 R over 77 days

Because the lesion appeared to become smaller during the treatment a further attempt at radical removal was decided upon and performed in August 1961 through a thoraco abdominal incision The tumour was now found to be encapsulated and apparently well separated from surrounding structures thus making complete removal possible The left kidney and adrenal transverse colon and spleen were also excised No lymph gland metastases could be found Different parts of the tumour presented variable histologic features Cells with marked nuclear polymorphism predominated but no mitoses were seen Some regions of the mass had the appearances of a fully differentiated sympathetic ganglion with

Table (*cont*)

Microscopy	VMA	Procedure	Results	Period of survival
a) Neuroblastoma b) Ganglioneuroma	—	Biopsy irradiation surgery	Alive and well	5 years
a) Neuroblastoma b) Ganglioneuroma	—	Biopsy irradiation	Died of intercurrent disease	21 years
a) Neuroblastoma b) Necrotic tumour tissue	+	Biopsy irradiation	Alive and well	3 years 11 months
Neuroblastoma	+	Surgery irradiation	Died	(2 years 5 months)
Neuroblastoma	—	Biopsy irradiation	Died	(3 1/2 months)
Neuroblastoma	+	Surgery irradiation	Died	(11 months)
Neuroblastoma	+	Biopsy irradiation	Died	(4 months)
Neuroblastoma	+	Biopsy irradiation	Died	(13 months)
Neuroblastoma	+	Surgery surgery irradiation	Alive and well	1 year 7 months

somewhat degenerate but otherwise normal looking nerve cells The histologic picture was now that of a ganglioneuroma

The patient has since been seen periodically in the out patients clinic but so far no signs of recurrence have been recorded at the control examinations

Case 2 A boy born in February 1941 who when 6 months old developed peri-orbital haemorrhages and swellings in both temporal regions At the age of 8 months when he was referred for radiotherapy a large abdominal mass with areas of calcification was present Metastases in the orbital bones with periosteal thickening were causing exophthalmos Metastases were also observed in the mandible Biopsy from above the left eye revealed neuroblastoma tissue

Both temporal regions and the right side abdominal tumour were irradiated with 600 900 and 950 R respectively The patient's general condition improved during and after the treatment The swelling over both eyes the exophthalmos and the abdominal tumour al

became smaller A second course of radiotherapy with somewhat smaller doses was given a few months later

In 1946 the patient was re admitted with an unusual swelling in the right parietal region Radiography revealed numerous small areas of calcification in the abdominal lesion A further course of irradiation was given to the deposits in the skull

In 1951 radiography showed no significant changes in the appearance of the skull but areas of filling defects were observed in some of the ribs and vertebrae as well as in the left scapula and pelvis The right kidney was slightly displaced The cranial deposits were again irradiated but the treatment was discontinued when biopsy failed to reveal any malignant tissue

The patient was again admitted to hospital in 1962 this time with a perforated gastric ulcer At operation a retroperitoneal tumour 10 cm in diameter and adherent to surrounding tissues was found Tumour cells at the site of perforation could not be excluded by micro scopy and the patient was again referred to our Centre in February 1962 Assuming that the tumour was again active conventional irradiation with 250 kV to large opposing fields was given to the abdomen over a period of 29 days covering a total dose of 1 696 R

The patient was well when discharged but in June 1962 was admitted to his local hospital with haematemesis and he died 3 weeks later The post mortem examination revealed a large gastric ulcer and a well demarcated retroperitoneal ganglioneuroma Metas tases of similar tissue were present in the lumbar thoracic and cervical lymph nodes and a small deposit in the vertebra Th 8 There was no evidence of cranial deposits Microscopy of the primary tumour and of the lumbar and thoracic deposits revealed uniform appear ances of ganglioneuroma No neuroblastoma tissue was observed

Case 3 A girl born in January 1962 who when 8 months old developed a lump under the left arm She was referred to the Tuberculosis Clinic where roentgen examinations revealed a large fairly well demarcated tumour posteriorly in the left lung The lesion filled about half the left thoracic cavity and involved the 2nd to 8th ribs The mediastinum was displaced to the right A firm irregular elastic and fairly mobile tumour measuring 3 cm × 2 cm × 2 cm was felt in the left axilla Subsequent needle biopsy at the Radium Centre indicated that the tumour was a neuroblastoma

Treatment was begun with conventional radiotherapy (250 kV) to opposite fields to in clude the whole left part of the thorax mediastinum and left axilla A total dose of 5 100 R was given during a 39 day period between October—November 1962 This represented a calculated tumour dose of 4 182 R The patient was not unduly upset by the treatment and on the 38th day of treatment there was a slight reduction in tumour size Following the irradiation two metastases in the left axillary lymph nodes were removed surgically these tumours contained malignant tissue with large necrotic and haemorrhagic areas but there was no sign of any transition to ganglioneuroma The patient was discharged a week later and followed up in the out patients clinic

About ten months later the child was said by the mother to be listless irritable and crying a lot Control roentgen examination showed that the left chest was now normal apart from some small areas of calcification and certain structural alterations in the vertebrae which could have resulted from the earlier irradiation The child was re admitted for observation for a period of 12 days The V M A excretion was pathologically raised (40—25—25—35 μg/mg creatinine) and the fluorimetric estimation of adrenaline/nor adrenaline excretion was 32 μg/24 hours This value is above that normally expected for a subject of this body weight There being no indication for further radiotherapy the patient was discharged and

closely followed up in the out patients department The V M A excretion later fell to normal limits and the child has since remained in good health

Case 9 A girl born in June 1964 was admitted to hospital when just under 2 months old because of failure to thrive and apparent inability to move the legs Myelography disclosed a large subdural tumour in the thoracolumbar part of the spinal canal

Laminectomy from D9 to L1 was performed in December 1964 and the tumour occupying the spinal canal was excised A more radical attempt at complete removal was made a fortnight later through a left side paravertebral thoracolumbar incision The retroperitoneal muscles were infiltrated with malignant tissue which was also spreading up through the diaphragm into the posterior mediastinum Radical removal was impossible The growth was proved histologically to be a neuroblastoma

The patient was later transferred to the Radium Centre The V M A excretion when measured the first time was 58 μg/mg creatinine The posterior thoracic wall was then irradiated over a wide area with a cobalt machine (mobaltron) The central tumour dose calculated to a depth of 4 cm was 3 655 R over 51 days The patient was very upset by the irradiation lost weight and vomited frequently during the period of treatment The V M A excretion fell steadily to reach normal values about a month after treatment had been stopped 28—32—21—16—21—8 μg/mg creatinine

There was free movement of both legs on discharge The child has since been admitted a number of times for assessment There is no evidence of recurrence and the weight is slowly increasing The left leg is however 2 cm shorter than the right and in spite of physiotherapy she is still disinclined to bear weight on it The V M A excretion is now normal

Discussion

It is not the purpose of the present paper to deal with the clinical aspects of neuroblastoma These are discussed exhaustively in a number of recently published papers e g DARGEON (1962) A few topics of special interest will however be mentioned

Composition of the material When interpreting the results of treatment two significant points stand out First the age distribution This in the present series is roughly in accordance with that found by other workers (e g STOWENS 1957) Most cases occur in the first two years of life and it is this group that has the best prognosis Secondly the presence of metastases is noteworthy As may be seen from the Table the material was highly selected all cases having widespread metastases at the time of treatment The condition usually presents with non specific signs or those resulting from distant metastases In both instances a long interval frequently elapses before the diagnosis is made The histologic appearances and V M A excretion usually clinch the diagnosis

Histologic aspects The picture presented by a neuroblastoma may be characteristic but this is far from always so The tumour cells vary considerably in size

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Case 3 A girl born in January 1962 who when 8 months old developed a lump under the left arm She was referred to the Tuberculosis Clinic where roentgen examinations revealed a large fairly well demarcated tumour posteriorly in the left lung The lesion filled about half the left thoracic cavity and involved the 2nd to 8th ribs The mediastinum was displaced to the right A firm irregular elastic and fairly mobile tumour measuring 3 cm × 2 cm × 2 cm was felt in the left axilla Subsequent needle biopsy at the Radium Centre indicated that the tumour was a neuroblastoma

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About ten months later the child was said by the mother to be listless irritable and crying a lot Control roentgen examination showed that the left chest was now normal apart from some small areas of calcification and certain structural alterations in the vertebrae which could have resulted from the earlier irradiation The child was re admitted for observation for a period of 12 days The V M A excretion was pathologically raised (40—25—25—35 μg/mg creatinine) and the fluorimetric estimation of adrenaline/nor adrenaline excretion was 32 μg/24 hours This value is above that normally expected for a subject of this body weight There being no indication for further radiotherapy the patient was discharged and

monograph entitled Neuroblastoma — Biochemical studies (edited by Bohuon) has recently been published (1966) containing articles dealing with the biochemistry of this condition The estimation most commonly used is that of the vanilmandelic acid (3 methoxy 4 hydroxy D mandelic acid) This has been our routine practice since the end of June 1963, and a large number of analyses have been performed The estimation is primarily of value in establishing the initial diagnosis V M A estimations are also helpful in assessing the response to treatment this being directly reflected by the level of excretion The V M A estimation is furthermore of particular value in subsequent follow up examinations

The incidence of raised V M A excretion in neuroblastoma cases varies slightly with different workers but is in the order of 80 % Besides neuroblastoma abnormal values occur only with phaeochromocytoma a condition that does not usually enter into the differential diagnosis Values are expressed in the μg/mg creatinine estimated in the urine and when found repeatedly to be above 10 μg/mg must be considered abnormal In our Centre false positive or false negative results have not occurred with these criteria A significant rise is usually evident when the test is positive and may be very high indeed in patients who are gravely ill Terminal values for Cases 4 6 7 and 8 were between 500 and 600 μ/mg creatinine

Results of treatment in different series Three basic methods namely surgery radiotherapy and chemotherapy are available for the treatment of neuroblastoma A number of large series have now been published but comparison of the results is difficult The material is often selected and in most instances various methods of treatment have been combined and used in different ways Furthermore not all authors have taken into account the age distribution of their cases a highly significant factor when interpreting findings A few of the larger series are referred to below

WITTENBORG (1950) described 73 cases 30 % of which survived 3 years or more Of 28 untreated cases three (10 %) survived at least 3 years 45 cases were treated with (1) surgery (2) surgery and post operative radiotherapy or (3) radiotherapy alone The 3 year survival figure for 11 cases without metastases treated by surgery alone was 54 % (6 cases) The 3 year survival for 9 cases without metastases treated with operation and post operative radiotherapy was 66 % (6 cases) The 3 year survival for 21 cases with metastases treated by radiotherapy alone was 28 % (6 cases)

PHILLIPS (1953) collected 155 cases from different hospitals The overall 3 year survival rate was 22 6 % HORN JR et coll (1956) followed 41 out of a total of 44 cases for 14 months twenty five of the patients died and sixteen

and appearance depending upon the degree of differentiation In the most undifferentiated tumours, the cells are darkly stained, resemble lymphocytes and measure about 10 μ in diameter They have large, dark nuclei and only little cytoplasm (sympathogonia) The cells may lie uniformly and close together with little stroma or in short lines of lumps Tendency to typical rosette formation strongly supports the diagnosis It is however common not to find this pattern, particularly in the more quickly growing tumours when the diagnosis may only be tentative According to STOWENS (1947), rosettes occur in about 15 % of all cases Large polygonal cells (sympathoblasts) may be present in the more highly differentiated varieties, these have more cytoplasm and their nuclei exhibit a less dense chromatin structure Fibril bundles are frequently seen in the stroma From this type of cell all intermediary stages up to a fully differentiated ganglion cell may be present Specimens taken from different regions may reveal various degrees of differentiation It has long been known that a neuroblastoma may regress spontaneously This process probably always begins with haemorrhages, tissue necrosis and small areas of calcification, although these changes do not usually occur uniformly throughout the tumour, the macroscopic appearances often being just as variable as the microscopic ones Similar changes also frequently precede the very characteristic process of maturation which a malignant neuroblastoma may undergo, resulting in a benign ganglioneuroma This phenomenon was first described by CUSHING & WOLBACK (1927) Areas of ganglioneuroma tissue containing fully differentiated ganglion cells are frequently to be seen in a neuroblastoma and explain the various descriptive terms used in the histologic diagnoses neuroblastoma, ganglioneuroblastoma and ganglioneuroma The maturation of a neuroblastoma to a ganglioneuroma may like its regression, occur either spontaneously or following the treatment This process was seen to occur histologically in Cases 1 and 2 of the present series There are some reports in the literature (e g KOOP & HERNANDEZ 1964, UHLMANN & VON ESSEN 1955) of a malignant form of ganglioneuroma producing metastases composed of ganglioneuroma tissue but in which neuroblastoma cells may also occur It is however doubtful whether such an interpretation is correct It would seem more reasonable to suppose that in such cases the primary tumour is a neuroblastoma, the metastases of which have either changed or are in the process of changing to benign ganglioneuroma cells

Vanilmandelic acid excretion with neuroblastoma The discovery by MASON et coll (1957) that the urinary excretion of adrenaline and nor adrenaline was increased in cases of neuroblastoma inaugurated examinations of the urine for cathecholamines It was soon found that a number of catecholamine metabolic breakdown products could be demonstrated in varying amounts in the urine A

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survived symptom free. This author advocated operative treatment which should be as radical as possible. STOWENS (1957) collected a series which included 105 cases of neuroblastoma. Fourteen of the patients survived 18 months or more; the author emphasized that all these except one were under one year old. KOOP & HERNANDEZ (1964), out of a series of 86 neuroblastoma cases, had 31 survivals for 14 months or longer. These authors recommended surgery and found that the mortality is higher among patients who have also had radiotherapy as compared to those treated by surgery alone. UHLMANN & VON ESSEN (1955) gave details of 20 cases, all of which underwent radiotherapy: seven of the patients survived from 22 months to 13 years. All were treated only by radiotherapy after diagnostic biopsy; five had metastases at the time of treatment.

The present series is small compared to those described above. As already stated, every case had metastases at the time of treatment. In spite of this, the disease was seemingly controlled in four out of nine cases. The patients were 14.5, 8, 9 and 5 months old, respectively, when treatment began. This is in agreement with the findings of all other workers, the prognosis being far better for very young children. The percentage restored to health falls sharply if the condition manifests itself after the second year of life. We first believed that Case 4 had recovered, as the patient remained symptomfree for a long time and the V.M.A. excretion was normal. The course of the disease is usually much quicker than this, and if symptom free for a year the patient usually recovers.

A number of factors must be considered when assessing the different series. By far the largest number of cases has been treated primarily by surgery. When the growth was thought to have been completely removed this was generally the only form of treatment given. When radiotherapy was applied, this often meant that either metastases were already present or that complete removal of the tumour was thought impossible. A true comparison of these two forms of treatment is therefore not usually possible.

Surgical treatment. Traditional surgical removal of the primary growth is usually attempted provided the lesion is considered operable and no metastases are present. It frequently happens however that it only becomes evident at operation that complete removal of the mass is impossible due to infiltration of neighbouring structures. If this happens, two possible courses of action are open to the surgeon. Either he must abandon the operation, in which event treatment must be primarily by radiotherapy and if circumstances permit a further attempt at operation be made later. This was the course adopted in the first case of the present series. The other alternative is to continue and remove as much of the tumour as possible even though this may mean a major surgical

procedure The considerations are in principle much the same when the surgeon decides to operate on a neuroblastoma in the presence of metastases Experience has shown that in certain cases in which a large (or small) operation has been performed without it being technically possible to remove the growth completely the child has nevertheless survived KOOP & HERNANDEZ (1964) for example in their collection of 31 surviving cases described no less than 8 cas s in which surgery was described as inadequate and in which no further therapy was given These phenomena are far from being clearly understood It is known that neuroblastoma may regress spontaneously in from 2 % to 10 % of cases Like wise as already described in this paper neuroblastomas have the property of maturation to a benign ganglioneuroma. Furthermore certain observations would suggest that the so-called metastases found in this condition are in fact multiple primary foci (DARGEON 1962 KNUDSON & AMROMIN 1966) It is doubtful how much significance can be attributed to these various factors in such a case re covering after only partial removal of the tumour Knowledge of the natural history of neuroblastoma is still far from complete At the moment though the practical deduction must be that the presence of metastases or a technically in operable tumour does not contra indicate operation

There are however other factors to be taken into account Any operative interference with a malignant tumour is attended by the risk of spread of tumour cells Surgery will also complicate subsequent radiotherapy a major operation delaying this for many days The risk of such a delay must be weighed most riously when dealing with neuroblastoma where time is of utmost im portance

Radiotherapy In ass ssing the available literature on radiotherapy of neuro-blastoma it must be remembered that almost without exception it is concerned with cases that were either primarily considered inoperable or for which at op ration radical surgery was found to be impossible It is estimated that 50 % of neuroblastomas have attendant metastases at the time they present No suf ficiently large material is available upon which to judge the results to be obtained by radiotherapy alone on localized (operable) neuroblastomas without metas-tases There is reason to believe however that these results may be exceptionally good

The principles upon which the irradiation of neuroblastoma is based are broadly similar to those governing the treatment of other malignant tumours To include all the tumour tissue the fields often have to be very large and unpleasant radiation effects on the general condition may limit the amount of irradiation given and make it impossible to attain the desired tumour dose This may also cause the treatment to be prolonged The actual tumour dose depends

on many factors but the tendency in recent years has been for it to increase. A calculated tumour dose of from 4 000 to 5 000 R would probably be reasonable. High voltage therapy is usually preferred today.

All are agreed that the radiation treatment of neuroblastoma demands an active procedure also in advanced cases with wide-spread metastases. Cases in which it was impossible to give adequate irradiation to all the tumour tissue because of the distribution and position of metastases have been seen to survive. Even malignant tissue, although untreated itself, has been known to disappear, become calcified or undergo maturation following irradiation of other areas of the growth. In this respect experience obtained in radiotherapy thus seems analogous to that recorded in surgery.

Chemotherapy. Chemotherapy has been used in the treatment of advanced cases. A large number of drugs, including steroids, methotrexate, vincristine, nitrogen mustard, actinomysin D, vincaleukoblastine, cyclophosphamide, and B_{12} have been tried. Cyclophosphamide has probably given the best results. THURMAN et coll. (1964) described their experiences with this agent in a carefully planned study in which nine paediatric centres took part. The treatment was undertaken in cases of tumours, the size of which could be measured. The condition was clinically progressive in all cases and no longer amenable to surgery or roentgen therapy. Out of a total of 24 cases, the response was described as 'good' in ten cases and 'fair' in nine; no response was obtained in five of the cases. The improvement in the 19 cases lasted from one to over 20 months.

Cyclophosphamide in common with most of the other drugs mentioned above is toxic in therapeutic doses. Amongst a number of side effects leukopenia, gastro-intestinal symptoms and haemorrhagic cystitis commonly occur. These serious sequelae may obviously complicate the accomplishment of radiation treatment. It would therefore seem reasonable to reserve chemotherapy for cases no longer amenable to surgery and radiotherapy and in which the condition is progressive.

B_{12} treatment will be discussed only briefly. BODIAN et coll. (1953—1961) used large doses of B_{12} over long periods in children suffering from neuroblastoma who were also having conventional treatment. This treatment has been tried in many parts of the world. A number of reports in the literature suggest that B_{12} is without therapeutic effect. KOOP & HERNANDEZ (1964) stated that their results, when comparable with BODIAN's for size and age distribution, represented a better survival rate without B_{12} than BODIAN obtained. SAWITSKY & DESPOSITO (1965) in their report seemed finally to have discredited the use of B_{12}. A study of 103 cases covering a number of American hospitals was designed to

test the effectiveness of B_1 The results suggest that the remission rate was not increased either when B_1 was used alone or when it was combined with irradiation or with other chemotherapeutic agents

Conclusion

The present state of our knowledge makes it impossible to lay down definite rules concerning the best method of treating neuroblastoma Each case should be assessed by both the surgeon and radiotherapist before treatment is begun There can be little doubt that treatment should take place in a few specialized centres if the best results from surgery and high voltage therapy are to be obtained Although each case should be individually assessed it may be helpful to lay down certain broad principles upon which the treatment of different categories of neuroblastoma can be based

Operable tumour without metastases The treatment is by tradition surgical (No sufficiently large material is available to evaluate radiotherapy alone in such cases) Surgery should be supplemented by radiotherapy

Inoperable tumour without metastases Two possibilities are available (1) irradiation initially followed in some cases by surgery (2) operation to remove as much malignant tissue as possible followed by irradiation

Operable tumour with metastases Perhaps surgical removal of the tumour followed by radiotherapy to the operation site and to as many metastases as possible

Inoperable tumour with metastases Radiotherapy to both primary tumour and metastases

Chemotherapy should be considered in cases no longer amenable to surgery or radiotherapy and where the condition is progressive Cyclophosphamide seems to be the most satisfactory drug available at present

SUMMARY

The treatment of neuroblastoma based upon a 5 year material is discussed Inability to remove the tumour completely does not contra indicate operation Irradiation should be performed actively recovery had occurred where it was impossible to irradiate the whole growth Chemotherapy should be considered only when surgery or radiotherapy is no longer possible

ZUSAMMENFASSUNG

Eine Übersicht über die Behandlung des Neuroblastomes wird anhand eines 5jährigen Materials gegeben Auch wenn die totale Entfernung des Tumors nicht möglich ist sollte die Operation vorgenommen werden Eine aktive Strahlenbehandlung ist notwendig Heilung erfolgte auch wenn es nicht möglich war die ganze Geschwulst zu bestrahlen Die Chemotherapie sollte nur dann angewandt werden wenn Chirurgie und Strahlentherapie nicht mehr möglich sind

RÉSUMÉ

L auteur etudie le traitement du neuroblastome en se basant sur son materiel de 5 ans L impossibilite de faire une exerese complete de la tumeur ne contre indique pas l operation Il faut faire une irradiation importante des guerisons ont eu lieu dans des cas ou il etait impossible d irradier toute la tumeur On ne doit envisager la chimiotherapie que quand la chirurgie ou la radiotherapie ne sont plus possible

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FROM THE DEPARTMENTS OF RADIATION PHYSICS (DIRECTOR K LIDEN) RADIO THERAPY (DIRECTOR M LINDGREN), ROENTGEN DIAGNOSIS II (DIRECTOR O NORMAN) AND PATHOLOGY (DIRECTOR C C AHLSTROM) UNIVERSITY OF LUND, SWEDEN

CONTINUOUS RECORDING OF TRANSMISSION DURING ROENTGEN IRRADIATION OF OESOPHAGEAL CARCINOMA

by

U B NORDBERG H HENRIKSON T LANDBERG H OLIVECRONA and P O WEILAND

The net effect of various factors on the daily target dose may be followed by continuous measurement of transmission Exact knowledge of the dose received by the oesophagus is desirable in the irradiation treatment of oesophageal cancer as the difference between the dose required and overdosage is very small (EBENIUS et coll 1963) The dose may be assessed by calibrated transmission measurement (NORDBERG 1962 1967) In the present study the individual variation in transmission was recorded continuously during the whole course of treatment

Material and Method The material consisted of all the 46 patients (32 men and 14 women) who had received rotation treatment of oesophageal cancer in 1961 and 1962 Treatment was given by the rotation method (GYNNING 1951, GYNNING & LINDGREN 1965) with 200 kV and HVL 0 7 mm Cu once a day for 6 days a week The aim was a dose of 200 rad in the middle of the target per treatment the total maximum dose being 6 200 to 6 400 rad The geometric breadth of the field at the axis of rotation was 5 cm in 15 patients 6 cm in 30

Submitted for publication 17 March 1967

RÉSUMÉ

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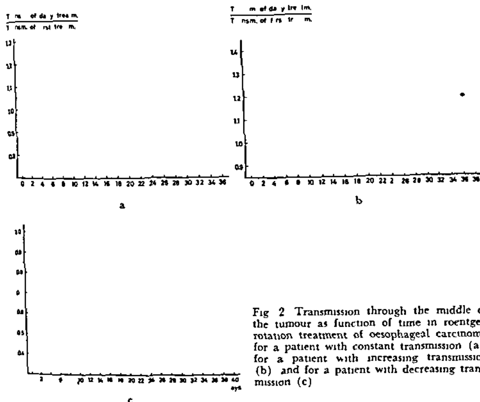


Fig 2 Transmission through the middle of the tumour as function of time in roentgen rotation treatment of oesophageal carcinoma for a patient with constant transmission (a) for a patient with increasing transmission (b) and for a patient with decreasing trans mission (c)

and 7 cm in one patient The field used was 6 cm longer (3 cm cranially and 3 cm caudally) than the roentgenologic length of the tumour The treatment was administered under continuous fluoroscopic supervision all necessary corrections of the beam being made during the irradiation The patient was instructed to swallow about 5 ml of a barium sulphate suspension at a given signal This was repeated four to eight times during each sitting The entire series of treatments of a given patient was usually performed by the same radiologist which facilitated geometric reproducibility

A flat ionisation chamber divided into several sections allowing determination of the transmission simultaneously at seven levels was fastened to the tube side of the fluoroscopic screen (NORDBERG 1962 1967) The middle section of the chamber was placed at the level of the roentgenologic centre of the tumour The transmission was as a rule measured six times a week and never less often than twice a week and constituted the integrated mean value for a complete



a



b



c

Fig 1 Histologic grading of oesophageal carcinoma Stain haematoxylin and eosin × 250 a) Highly differentiated squamous cell carcinoma with intercellular bridges and horny pearls b) Moderately differentiated tumour still recognizable as a squamous cell tumour but with little or no keratinization c) Low differentiated carcinoma composed of anaplastic cells without epidermoid characteristics

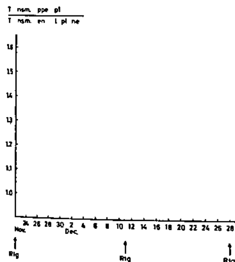




Fig 3 Ratio between transmission through upper plane of area treated and through central plane as function of time in roentgen rotation treatment of a patient with oesophageal carcinoma and roentgenograms of the same patient at the dates indicated in the diagram The dose in middle of the tumour was 800 rad on 28 November and 3 600 rad on 14 December

patients In the four patients with prestenotic dilatation the ratio between the transmission in the upper plane and that in the middle plane increased during treatment (Fig 3) In the other four patients with stenosis but without prestenotic dilatation the ratio was constant In the eight patients without stenosis the ratio was constant in six and increased in two

The increase of the transmission in the upper plane in relation to that in the middle plane in patients with severe stenosis and prestenotic dilatation was presumably due to regression of the tumour and consequently more rapid passage of the contrast medium and decreased degree of dilatation But this alone does not suffice to explain the variation in transmission during treatment since the ratio between the transmission in the upper and the middle planes also increased continuously in two of the patients without stenosis Since the middle of the

revolution The dose to the oesophagus was measured by eight small condenser chambers in a catheter that was passed down the oesophagus Such measurements were usually made four times during the first third of the treatment period and sometimes also later

The oesophagus was always examined roentgenographically immediately before radiotherapy was started, in the middle of the course of treatment, and after its conclusion At examination of the roentgenograms, notes were made of *the initial roentgenologic length of the tumour*, severity of stenosis, irregularities of the mucosa, as well as any regression of the pathologic changes during treatment

All the biopsy specimens were reviewed and the tumours were graded into the three histologic categories of squamous cell carcinoma (Fig 1) the highly differentiated, the moderately differentiated and the undifferentiated or anaplastic types Biopsy had not been performed in two patients, and in two others no biopsy specimens were available from the primary tumour, these patients were therefore classified according to the appearance of the metastases All of the tumours were graded according to their least differentiated components

Results and comments

In eight patients, the transmission measurements were unreliable, or too few, and these patients were therefore not included in the analysis

The transmission through the midplane of the tumour proved to be constant in eight patients during the entire period of treatment (Fig 2a) It varied in 30 patients, in 22 of these the transmission tended to increase successively during the first third of the treatment period (Fig 2b) and in the remaining 8 patients *it tended initially to decrease* (Fig 2c)

For each of the 30 patients in whom the transmission varied, a final target dose was calculated on the basis of the transmission determined during the first days, and this dose was compared with the true dose i e the dose calculated with due allowance for the variation of transmission The calculated dose was 4 % to 27 % (median 9 %) less than the true dose in those patients in whom an increase of the transmission was noted The calculated dose exceeded the true dose by 1 % to 11 % (median 8 %) in those patients in whom the transmission initially decreased

In 16 patients, the variation of the transmission was analysed not only at the level of the centre of the tumour but also in a plane 4 5 cm cranially *Eight of* these had stenosis, which in four patients was so marked that a prestenotic dilatation, in which the contrast medium accumulated at the level of the upper plane, was present, *the stenosis regressed during treatment* in all of these eight

mission caused by an equal change in the amount of water equivalent tissue in the section The roentgenologic middle of the tumour was situated at the level of the eighth thoracic vertebra i e the level where the amount of lung tissue is largest in ten of the 22 patients with increasing transmission but in only one of the 8 patients with decreasing transmission The presence of the mammary glands may decrease the relative amount of lung tissue in a section Sixteen men and six women belonged to the group with increasing transmission and five men and three women to the group with decreasing transmission

The change in transmission may also depend on variation in weight None of the patients in the group with increasing transmission gained weight during treatment ten kept their weight (± 2 kg) and eight lost weight (2 to 6 kg) In the group with decreasing transmission three patients gained weight (2 to 3 kg) during treatment, three kept their weight (± 2 kg) and one patient lost 3 kg

As regards other factors that may have influenced the transmission it should be mentioned that in one patient with increasing transmission the initially increased breadth of the mediastinum regressed during treatment and in another patient an initial pleural effusion decreased during treatment On the other hand pneumonia in one patient did not affect the steady increase in transmission The weights of all of these patients remained unchanged during treatment Pleural effusion supervened during treatment in one patient in the group with decreasing transmission the weight of the patient during treatment also remained constant

SUMMARY

The variations in the net effect of different factors on the daily target dose were studied by means of continuous measurement of transmission in 38 patients who received roentgen rotation treatment for oesophageal cancer In 8 patients the transmission in the middle of the tumour was constant in 22 it increased and in 8 it decreased The ratio between the transmission in the upper and in the central part of the area treated was studied in 16 patients and in six of these the ratio varied in the course of treatment

ZUSAMMENFASSUNG

Unter Benutzung kontinuierlicher Transmissionsmessungen wurden die Variationen der Einwirkung verschiedener Faktoren auf die tägliche Herddosis bei 38 Patienten die wegen eines Ösophaguskarzinoms mit Röntgen Rotationsbestrahlung behandelt wurden studiert Bei 8 Patienten war die Transmission in der Mitte des Tumors konstant bei 22 wurde sie erhöht und bei 8 herabgesetzt Das Verhältnis zwischen der Transmission im oberen und im zentralen Teil des Behandlungsgebietes wurde bei 16 Patienten studiert und bei sechs von diesen wurden im Laufe der Behandlung Änderungen dieses Verhältnisses registriert

Table

Distribution of histologic grades of oesophageal carcinoma among groups of patients with different types of variation in transmission during rotation treatment

	Different grades of histologic differentiation of oesophageal carcinoma			Total
	Highly differentiated	Moderately differentiated	Poorly differentiated	
Constant transmission	4	2	2	8
Increasing transmission	2	7	12	21
Decreasing transmission	1	4	2	7
	7	13	16	36

tumour is filled with contrast medium for only a short period of treatment, the absolute variation in transmission in this plane should not be influenced to any appreciable extent by its presence The following explanations therefore appear more likely

Of the 16 patients with poorly differentiated tumours, twelve belonged to the group with increasing transmission (see Table) One would expect such poorly differentiated cancers to be very radiosensitive and to regress quickly with a consequent increase in transmission in the tumour area In addition, the patients with intermediate type of tumours often, though less commonly than the poorly differentiated ones, belonged to the group with increasing transmission Only two of seven patients with highly differentiated tumours had increasing transmission

Tumours of considerable length may be wider than short ones, regression of the former would therefore mean a greater change in the amount of absorbing tissue In 19 patients, the tumours were roentgenographically longer than 4 cm Sixteen of these belonged to the group with increasing transmission and three to the group with decreasing transmission

If complete roentgenologic regression of pathologic changes implies good regression of the width of the tumour such patients may be expected to have increasing transmission The irregularities of the mucosa disappeared in eight of the 22 patients with increasing transmission and in five of the 8 patients with decreasing transmission Complete regression of stenosis in the area of the tumour was noted in six of 17 patients with increasing and in one of 7 patients with decreasing transmission

The greater the ratio between the amount of lung tissue and water equivalent tissue in a given transverse section of the chest, the greater the change in trans

FROM THE INSTITUTE OF EXPERIMENTAL BIOLOGY AND GENETICS THE
CZECHOSLOVAK ACADEMY OF SCIENCES PRAGUE CZECHOSLOVAKIA

COMPARISON OF RADIATION EFFECTS IN VITRO UPON CHROMOSOMES OF HUMAN SUBJECTS

by

MARIA KUCEROVA

The cause of an increased incidence of leukaemia in Down s syndrome and the appearance of both these diseases in certain families is far from having been clarified STEWARD et coll (1958) found a twenty fold increase in the incidence of leukaemia in mongoloid children when studying a large series of patients with leukaemia. The association of the two diseases has been stressed by many investigators (TOUGH et coll 1961, KIOSSOGLOU et coll 1963 ENGEL et coll 1964 LAHEY et coll 1964 HONDA et coll 1964)

The incidence of leukaemia accompanied by other congenital chromosome aberrations for example a D/D translocation has been reported by ENGEL et coll (1965) chromosome mosaicism of XO/XXX type by LEWIS et coll (1963)

Mongolism and other congenital chromosome aberrations and leukaemia are known to occur in the same sibships (MILLER et coll 1961) In individuals trisomic for chromosome 21 *another* congenital chromosome aberration has in some cases been noted to occur at the same time (ZERGOLLERN et coll 1964 GRIPENBERG & VAIRAKKINEN 1964 DEKABAN et coll 1966) It appears that a certain chromosomal instability exists in individuals with congenital chromosome aberrations or in their families This assumption is supported by the findings of JACOBS et coll (1961) which indicated that individuals with congenital chromosome aberrations have a greater proportion of cells with a non modal number of chromosomes among their lymphocytes than individuals with normal karyotypes

Submitted for publication 1 December 1966

RÉSUMÉ

Les auteurs ont etudie les variations de la transmission au milieu de la tumeur au cours du traitement chez 38 malades traités par roentgentherapie pour cancer de l oesophage La transmission est restee constante chez 8 malades a augmente chez 22 et a diminue chez 8 malades Le rapport entre la transmission a la partie superieure du volume traite et celle du milieu de la tumeur a varie au cours du traitement chez 6 malades sur 16

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Table 1

Group results from karyological analysis of irradiated and non irradiated lymphocytes in normal individuals with trisomy of the 21st chromosome

Group	Number of mitoses with chromosome numbers			Number of all mitoses
	Hypo modal	Modal	Hyper modal	
Normal non irradiated	14	79	2	95
Normal after irradiation 300 R	34	80	17	131
Trisomic non irradiated	54	319	45	418
Trisomic after irradiation 300 R	140	122	37	299

One of the possible causes of this chromosomal instability might be an increased sensitivity to the noxious effects of the external environment

The purpose of the present investigation has been to ascertain whether a cell with an abnormal chromosomal arrangement has a changed sensitivity, most probably an increased sensitivity to ionizing radiation We attempted to demonstrate this by irradiation in vitro of trisomic cells and normal cells in short term *peripheral blood lymphocyte cultures*

In the experiments now reported we tried to find out (1) whether the cells trisomic for chromosome 21 have a sensitivity to irradiation in vitro which is different from the one in cells with a normal number of chromosomes, (2) whether the proportion of modal and non modal cells is different in trisomic and normal individuals after irradiation in vitro, (3) whether the type and number of postirradiation aberrations are different in both groups, (4) whether a certain group of chromosomes is more frequently affected by loss or increase of chromosomes in aberrant mitoses after irradiation, (5) whether the difference in the number of polyploid cells between the two groups of individuals examined is *significant after irradiation*

Material and Methods Peripheral blood lymphocyte cultures were prepared by the method of MOORHEAD et coll (1960) with slight modifications Peripheral blood lymphocytes were obtained from five human male donors below 10 years of age, with normal karyotypes, and from five individuals of the same age and sex, trisomic for chromosome 21 and showing clinical signs of Down s syndrome None of the boys was irradiated before the experiment except for the usual diagnostic roentgen exposure

From each of ten individuals the culture of lymphocytes was divided into two

Table 1 *(cont)*

Number of aberrant mitoses	Percent of aberrant mitoses	Number of all aberrations	Types of aberrations			Number of polyploid and endored
			Simple	Complex	Monotrisomic	
3	3 1	3	1	1	1	—
37	28 2	93	26	48	19	22
7	1 67	7	5	1	1	9
168	56 1	308	124	135	49	57

samples and cultured for 18 hours in separate bottles Thereafter a half of all the cultures was exposed to 300 R of gamma irradiation from a cobalt 60 source (Theratron B 41 R/min) All the cultures both irradiated and non irradiated during this manipulation were left for an hour at room temperature

After 69 hours of growth in culture, i.e 51 hours after irradiation Colcemide (Ciba) (diacetyl N methyl colchicin) in 2 gamma/ml concentration was added to all cultures The total cultivation time was 72 hours

The cultures were treated as usual All satisfactory mitoses were photographed cut and scored

From the qualitative point of view the chromosomal aberrations have been classified into the following three categories

1 *Simple* (resulting from a simple chromosome or chromatid breakage) chromosome and chromatid breaks deletions fragments (simple and double) gaps (not assigned to any group at all)

2 *Complicated* (resulting from multiple breakages) dicentric chromosomes ring chromosomes chromosomes abnormal in shape different types of translocations

3 *Mono trisomy* (possibly resulting from multiple translocations inversions and deletions or non disjunctions and loosing) i e cells in which the chromosomes cannot be assigned with certainty in normal number to groups according to the Denver nomenclature but otherwise have a normal shape

The significance of differences of two frequencies was shown using the formula

$$u = \frac{h_1 - h_2}{\sqrt{h(1-h)\left(\frac{1}{n^1}+\frac{1}{n^2}\right)}}$$

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From each of ten individuals, the culture of lymphocytes was *divided into two*

Table 2 *(cont)*

Isochromatid break	Anomal chromosome	Monotrisomy	Ring chromosome	Translocation
1	17	49	3	2
0 3	5 5	*15 5*	0 9	0 6
—	3	16	3	2
—	3 6	*19 5*	3 6	2 4

chromosomal groups The reverse is true in the group 16—18 but this increase took place at approximately the same rate in both groups of individuals under study

After irradiation several aberrations were frequently accumulated in individual mitoses but to the same extent in individuals of both groups

We have found that the percentage of polyploid mitoses does not differ in a set of irradiated cells from individuals of both groups ($P > 0\,05$) but it is significantly higher ($P < 0\,001$) when compared with the number of polyploid cells in non irradiated mitoses from individuals of both groups

Discussion

While our experiments were in progress the results of two groups of investigators DEKABAN et coll (1966) and CHUDINA et coll (1966) were published These authors were also concerned with the question whether the cells trisomic for chromosome 21 are more sensitive to irradiation in vitro

The results of DEKABAN et coll showed a higher but not significant incidence of aberrations in trisomic cells after irradiation *in vitro* They irradiated the lymphocytes with 100 R of roentgen rays A comparison of their results with our observations is however difficult because part of the cells were irradiated as late as at 68 hours of culture i e 4 hours before the end of culture and the other part before the commencement of culture

The same difficulty is encountered when comparing our results with those of CHUDINA et coll who likewise observed a higher but insignificant incidence of aberrations in trisomy after irradiation in vitro They used doses of 10 20 and 40 R roentgen irradiation and like DEKABAN et coll irradiated the cells at 68 hours of culture and 4 to 5 hours before the end of culture

Table 2

Individual types of observed postirradiation chromosomal aberrations

Group		Dicentric chromosomes	Difragment	Fragment	Chromatid break
Trisomy	Number of aberrations	117	94	18	5
	Percent	37 9	30 5	5 8	1 6
Normal	Number of aberrations	31	29	1	1
	Percent	37 7	35 3	1 2	1 2

Results

The results of a karyological analysis are presented in Table 1 The percentage of aberrant mitoses after irradiation with 300 R in vitro is higher in individuals trisomic for chromosome 21 than in those with normal karyotypes and this difference is highly significant ($P < 0\ 001$)

The study of the percentage of mitoses with the modal, hypo and hyper modal number of chromosomes in trisomic and normal individuals before and after irradiation in vitro showed that the number of cells with the modal number of chromosomes is but insignificantly lower in trisomic individuals already before irradiation After irradiation, the decline is more marked in trisomic individuals than in normal individuals The proportion of modal cells in trisomic individuals is significantly (highly) lower than before irradiation ($P < 0\ 001$)

The decline in the number of modal cells takes place in favour of mitoses with the hypomodal number of chromosomes This finding may suggest an increased fragility of trisomic cells after irradiation

It is evident from a detailed analysis of postirradiation aberrations in the two groups under study that qualitatively they do not differ significantly from each other, and also the percentual proportion of the invidual types of aberrations is not different This proportion is illustrated in Table 2 which shows that the most frequent aberration following the given radiation exposure in vitro was the dicentric chromosomes, difragments and mono trisomy The other types of aberrations were less frequent

A study of the quantitative changes in the chromosomes in aberrant mitoses showed that certain groups of chromosomes were not affected in a very different manner in individuals of both groups as shown in the accompanying figure It can be seen that loss of chromosomes prevails over their increase in all the

the cells in an early stage of DNA synthesis After irradiation at 68 hours of culture they were probably in the late stage of DNA synthesis

We observed a significantly higher percentage of aberrations in trisomic cells after irradiation even though the cells were irradiated in the G1 phase or in the early S phase which are less radiosensitive than the late S phase of G2 phase as reported by CHU et coll (1961) and by BREWEN (1965)

It thus appears that the statistical significance of our results is due to the more abundant material at our disposal and not to the higher biological sensitivity of cells to irradiation performed at different time intervals of culture

SUMMARY

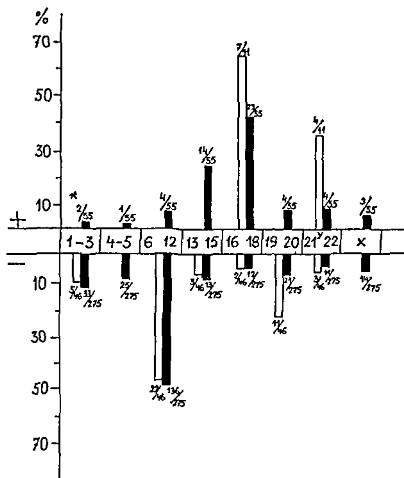
The culture of lymphocytes from five healthy individuals and five individuals with trisomy of the 21 chromosome was treated with 300 R from a cobalt 60 source at 18 hours of culture 54 hours before its end The results of karyological analysis of irradiated cells were compared with those of non irradiated lymphocytes from the same individuals. A significantly higher incidence of postirradiation chromosome aberrations and a greater decrease in number of modal cells after irradiation was found in trisomic cells The difference between the type of aberrations the losses of chromosomes and the number of polyploid cells was not significant

ZUSAMMENFASSUNG

Lymphozytenkulturen von funf gesunden Individuen und funf Individuen mit Trisomie des 21 Chromosomes wurden mit einer 300 R Kobalt 60-Quelle 18 Stunden nach dem Beginn der Zuchtung d h 54 Stunden vor dem Abschluss bestrahlt Die Ergebnisse der karyolovischen Analysen der bestrahlten Zellen wurden mit denen der nicht bestrahlten Lymphozyten von denselben Individuen verglichen. Nach Bestrahlung war die Anzahl der Chromosomen Aberration n signifikant hoher und bei den trisomischen Zellen wurde eine grosse re Reduktion in der Anzahl von modalen Z llen nachg wiesen Kein signifikanter Unterschied konnte zwischen den Aberrationstypen den Chromosomenverlusten und der Anzahl der Polyploidzellen festgestellt werden

RÉSUMÉ

Les cultures de lymphocytes de cinq sujets sains et de cinq suj ts atteints de trisomie du chromosome 21 ont été irradiees par 300 R d une source de cobalt 60 à la 18ème heure de la culture 54 heures avant sa fin Les resultats de l analyse karyologique des cellules irradiées ont ete comparès avec ceux de l analyse karyologique des lymphocytes non irradies du meme sujet On a constaté une frequence significativement plus elevee des aberrations chromosomiques après irradiation et une diminution plus importante du nombre des cellules modales apres irrad ations pour les cellules trisomiques Il n y avait pas de difference significative entre le type des aberrations les pertes de chromosomes le nombre de cellules polyploids des sujets sains et des sujets trisomiques



Distribution of losses and gains in chromosomes in trisomic and normal cells trisomic cells (black columns) determined by analysis of 299 mitoses normal cells (white columns) determined by analysis of 131 mitoses + additional chromosomes — missing chromosomes * numerator number of chromosomes in group denominator total number of chromosomes

The results of the above two groups of authors cannot therefore be compared with our observations The majority of aberrations obtained in both these groups after irradiation at 68 hours of culture were of the chromatid type This is due to the mitotic phase of cells at the time of irradiation In our experiments the aberrations of both chromosomal and chromatid type were observed but chromosome types predominated, as also noted by DEKABAN et coll after irradiation of cells before they were set in culture

According to BENDER & PRESCOTT (1962) and BREWEN (1965) our cells at 18 hours of culture were probably in the G1 phase, or possibly a small part of

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PROTECTIVE EFFECT OF CYSTEAMINE AT FRACTIONATED IRRADIATION

II Shortening of life span

by

ARNE NELSON OLA HERTZBERG and CURT RONNBÄCK

The results of a great number of animal experiments with chemical radioprotectors have proven that these agents protect against the acute manifestations of radiation injury Relatively few investigations refer to the protective effect against the more chronic consequences and after protracted and fractional radiation (STRAUBE & PATT 1963 DOULL et coll 1963 MAISIN et coll 1957 COSGROVE et coll 1965 MEWISSEN & BRUCER 1957 UPTON et coll 1959 HOLLCROFT et coll 1957)

The results of these investigations have however been equivocal An experiment was therefore designed to study the protective effect of cysteamine both at sublethal doses of fractionated irradiation up to accumulated doses in the lethal range and on the late effects among the survivors The results of the observations on the mortality up to 30 days after the last irradiation have been published in an earlier paper (NELSON et coll 1963)

Material and Methods Groups of inbred CBA male mice of about the same age (60 to 70 days) were exposed according to an irradiation schedule shown in our earlier paper (NELSON et coll) which also gives details of the irradiation as well as the other experimental conditions.

The mortality in all the experimental series was observed up to 30 days after the last irradiation The surviving animals in some series as well as the animals

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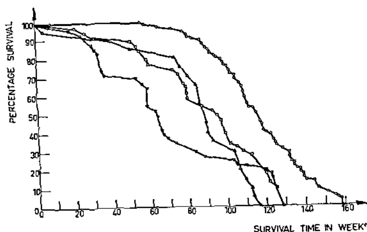


Fig 1 Mortal ty p tt n n un rrad ated control groups no treatment) ——— O I hy sal ne tw ce a week for l fe span □ ——— □ cyst mine tw c a w k for life sp n △———△ cysteam ne 4 mg/day < 24 ▽———▽

Results

The results of the experiments are presented in Tables 2 to 4 and Figs 1 to 11 They are reported upon in groups defined by a certain fraction dose a given interval and an accumulated exposure dose (AED) The life span is expressed in both mean and median survival times in weeks

I Unirradiated controls (Table 2 and Fig 1) The mean survival time in our unirradiated control series was 113 2 ± 2 52 weeks which is very close to the median survival time of 115 weeks saline as well as cysteamine influence sur vival The decrease in life span was likely due to the physical traumata caused by the repeated injections and the accumulated toxic effect of cysteamine

2 Fraction dose 160 R interval 7 days (Table 3 and Figs 2 3 and 4) In all the AED groups the protected mice had a longer mean survival time than the unprotected except in the highest exposure group (5 760 R) in which all animals except one died before the scheduled last irradiation (Fig 2) The tendency was the same regarding the median survival time

As an example of the distribution of deaths with time the mortality pattern of an accumulated exposure of 3 520 R is shown in Fig 3 The protected mice sur vived much longer than the unprotected The difference between the two slopes is obvious

In Table 3 the mean and median life span and in Fig 3 the mortality pattern

Table 1

Experimental schedule

I Unirradiated control series

Treatment	
1	None
2	Phys saline twice a week for life span
3	Cysteamine twice a week for life span
4	Cysteamine 4 mg/day × 24

II Irradiated series (50% of the animals in each group received cysteamine prior to irradiation)

Fraction dose (R)	Interval (days)	Accumulated dose (ALD) (R)
80	1	640 960 1280 1600 and 1920
80	3	Irradiation continued until all animals died
160	1	480 800 1120 1440 and 1760
160	3	1600 1920 2240 2560 2880 3200 and 3520
160	7	2880 3200 3520 3840 4160 4480 4800 and 5760 (No animals survived after this dose)

Table 2

Life span in mice unirradiated controls

Treatment	Number of animals	Mean survival time $\bar{x} \pm SE$ (weeks)	Median survival time (weeks)
None	95	113.2 ± [illegible].52	115
Phys saline two injections/week for life span	44	89.7 ± 4.75	96
Cysteamine 4 mg/twice a week for life span	42	72.1 ± 6.25	65
Cysteamine 4 mg/day × 24	20	85.1 ± 6.22	89

in the control groups (see Table 1) were observed for life span and tumour rate. In this paper, however, only the effect of cysteamine on the shortening of life span caused by irradiation will be reported.

The '80 R/3 days' series was treated differently from the others. Due to the low fraction dose and the interval of 3 days, no acute death, according to the mathematical model used in our previous paper, occurred (NELSON et coll.). The animals were irradiated until all died and half of them received a cysteamine injection prior to each irradiation.

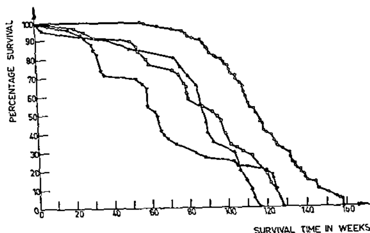


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As an example of the distribution of deaths with time the mortality pattern of an accumulated exposure of 3 520 R is shown in Fig 3 The protected mice survived much longer than the unprotected The difference between the two slopes is obvious

In Table 3 the mean and median life span and in Fig 3 the mortality pattern

Table 3

Life span of mice after fractionated irradiation protected by cysteamine (4 mg/animal) — Numbers in italics indicate protected groups — Numbers in brackets indicate animals missing during the experiments

Fraction exposure (R)	Time interval (days)	Accumulated exposure (R)	No of animals At beginning of irradiation	No of animals At end of irradiation	Time of first death (weeks)	Mean survival times x±SE (weeks)	Median survival (weeks)
160 (Series started 17 5 1961)	7	2 880	30	23 (2)	6	27 6±2 88	26
		2 880	*30*	*25 (3)*	*6*	*46 0±5 41*	*42*
		3200	30	27	12	26 2±2 11	22
		3200	*30*	*21*	*8*	*33 2±4 31*	*22*
		3 520	30	14	10	22 7±1 68	20
		3 520	*30*	*29* (3)	*13*	*52 6±4 62*	*50*
		3 840	30	5	9	20 0±0 77	19
		3 840	*30*	*14* (2)	*12*	*29 2±3 67*	*21*
		4 160	30	8	7	22 4±1 80	21
		4 160	*30*	*5*	*5*	*25 7±2 97*	*21*
		4 480	30	4	2	21 3±1 20	21
		4 480	*30*	*17*	*14*	*32 4±2 56*	*27*
		4 800	30	2	10	20 3±1 02	19
		4 800	*29*	*14*	*16*	*30 1±2 67*	*28*
		5 760	30	1	13	22 0±0 44	22
		5 760	*30*	*1*	*7*	*20 4±1 14*	*19*
160 (Series started 22 8 1961)	3	1 600	30	29	4	32 3±7 43	[illegible]
		1 600	*30*	*29* (5)	*1*	*45 2±9 14*	*26*
		1 920	29	20	5	7 90±1 26	6
		1 920	*30*	*28*	*2*	*42 5±7 22*	*13*
		2 240	30	6	5	5 6±0 13	[illegible]
		2 240	*30*	*24* (4)	*3*	*43 9±8 56*	*25*
		2 560	30	2	5	5 9±0 15	6
		2 560	*30*	*12*	*5*	*16 4±5 22*	*7*
		2 880	30	0	4	5 6±0 12	6
		2 880	*30*	*3*	*5*	*6 4±0 19*	*6*
		3 200	30	0	4	5 6±0 12	6
		3 200	*30*	*1*	*6*	*7 0±0 13*	*7*
		3 520	30	0	5	5 9±0 13	6
		3 520	*30*	*2*	*5*	*9 0±1 37*	*7*
160 (Series started 17 1 1962)	1	480	30	30 (3)	20	86 6±6 22	89
		480	*30*	*30*	*47*	*96 1±3 28*	96
		800	30	30 (2)	2	73 9±7 81	89
		800	*30*	*30* (1)	*2*	*101 2±4 47*	*105*
		1 120	30	30	2	7 3±3 44	3
		1 120	*30*	*30* (3)	*2*	*28 7±8 20*	*3*
		1 440	30	30	2	2 3±0 09	2
		1 440	*30*	*29*	*2*	*2 6±0 10*	*3*
		1 760	30	30	2	2 2±0 15	2

Table 4

Life span in mice after fractioned irradiation protected by cysteamine (4 mg/animal) — *Numbers in italics indicate protected groups* — *Numbers in brackets indicate animals missing during the experiments*

Fraction exposure (R)	Time interval (days)	Accumulated exposure (R)	No of animals: At beginning of irradiation	No of animals: At end of irradiation	Time of first death (weeks)	Mean survival time $\bar{x} \pm SE$ (weeks)	Median survival time (weeks)
80	1	640	30	30 (2)	4	89 1±5 16	93
(Series start		*640*	*30*	*27 (1)*	*1*	*83 7±6 86*	*94*
ed 13 2 1962)		960	30	30	3	87 7 ±5 59	89
		960	*30*	*29*	*2*	*98 4±5 60*	*106*
		1 280	30	30 (3)	3	75 6±8 54	90
		1 280	*30*	*23*	*2*	*53 1±8 09*	*48*
		1 600	30	27	3	13 9±5 01	4
		1 600	*30*	*17* (3)	*2*	*29 1±7 68*	*4*
		1 920	30	15 (2)	3	3 9±0 15	4
		1 920	*30*	*13*	*2*	*16 0±5 32*	*4*
80	1	640	30	30	27	85 2±4 34	89
(Series start		*640*	*30*	*26*	*1*	*84 6±6 59*	*96*
ed 3 5 1962)		960	30	30 (1)	3	55 9±9 14	62
		960	*30*	*27* (2)	*1*	*67 5±7 60*	*79*
		1 280	30	30 (5)	3	7 6±4 26	3
		1 280	*30*	*9*	*1*	6 5±2 96	*2*
		1 600	30	16	3	3 2±0 08	3
		1 600	*30*	*1*	*1*	*2 2±0 12*	*2*
		1 920	30	3	3	3 1±0 07	3
		1 920	*30*	*1*	*1*	*2 7±0 13*	*3*

from the beginning of the experiments i e the first irradiation are shown In order to get a more representative picture of the mortality pattern after the last irradiation the survival at different times has been calculated (see Fig 4) in per cent of the number of survivors at the end of irradiation It is obvious from these figures that the mortality rate in the protected group except at an AED of 5 760 R was much lower than in the unprotected group

3 Fraction dose 160 R interval 3 days (Table 3 and Figs 5 6 and 7) For the AEDs 1 600 R to 2 560 R the mean survival time was increased in the protected groups and so was the median survival time for the exposures 1 600 R to 2 240 R (Fig 5)

The mortality pattern at an AED of 2 560 R is presented in Fig 6 which

Table 3

Life span of mice after fractionated irradiation protected by cysteamine (4 mg/animal) — Numbers in italics indicate protected groups — Numbers in brackets indicate animals missing during the experiments

Fraction exposure (R)	Time interval (days)	Accumulated exposure (R)	No. of animals At beginning of irradiation	No. of animals At end of irradiation	Time of first death (weeks)	Mean survival times x±SE (weeks)	Median survival (weeks)
160 (Series started 17.5.1961)	7	2 880	30	23 (2)	6	27.6±2.88	26
		2 880	*30*	*25* (3)	*6*	*46.0±5.41*	*42*
		3200	30	27	12	26.2±2.11	22
		3200	*30*	*21*	*8*	*33.2±4.31*	*22*
		3 520	30	14	10	22.7±1.68	20
		3 520	*30*	*29* (3)	*13*	*52.6±4.62*	*50*
		3 840	30	5	9	20.0±0.77	19
		3 840	*30*	*14* (2)	*12*	*29.2±3.67*	*21*
		4 160	30	8	7	22.4±1.80	21
		4 160	*30*	*5*	*5*	*25.7±2.97*	*21*
		4 480	30	4	2	21.3±1.20	21
		4 480	*30*	*17*	*14*	*32.4±2.56*	*27*
		4 800	30	2	10	20.3±1.02	19
		4 800	*29*	*14*	*16*	*30.1±2.67*	*28*
		5 760	30	1	13	22.0±0.44	22
		5 760	*30*	*1*	*7*	*20.4±1.14*	*19*
160 (Series started 22.8.1961)	3	1 600	30	29	4	32.3±7.43	5
		1 600	*30*	*29* (5)	*1*	*45.2±9.14*	*26*
		1 920	29	20	5	7.90±1.26	6
		1 920	*30*	*28*	*2*	*42.5±7.22*	*13*
		2 240	30	6	5	5.6±0.13	5
		2 240	*30*	*24* (4)	*3*	*43.9±8.56*	*25*
		2 560	30	2	5	5.9±0.15	6
		2 560	*30*	*12*	*5*	*16.4±5.22*	*7*
		2 880	30	0	4	5.6±0.12	6
		2 880	*30*	*3*	*5*	*6.4±0.19*	*6*
		3 200	30	0	4	5.6±0.12	6
		3 200	*30*	*1*	*6*	*7.0±0.13*	*7*
		3 520	30	0	5	5.9±0.13	6
		3 520	*30*	*2*	*5*	*9.0±1.37*	*7*
160 (Series started 17.1.1962)	1	480	30	30 (3)	20	86.6±6.22	89
		480	*30*	*30*	*47*	*96.1±3.28*	*96*
		800	30	30 (2)	2	73.9±7.81	89
		800	*30*	*30* (1)	*2*	*101.2±4.47*	*105*
		1 120	30	30	2	7.3±3.44	3
		1 120	*30*	*30* (5)	*2*	*28.7±8.20*	*3*
		1 440	30	30	2	2.3±0.09	2
		1 440	*30*	*29*	*2*	*2.6±0.10*	*3*
		[illegible]	30	30	2	2.2±0.15	2

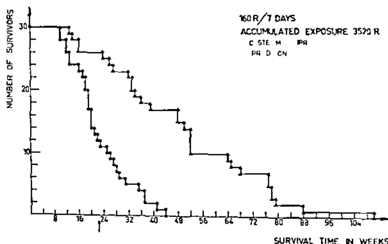


Fig 3 Mortality pattern in groups which had received 3 520 R Arrow indicates the last irradiation

6 *Fraction dose 80 R interval 1 day* (Table 4) The results in this series do not show any unequivocal differences in the means or the median life spans between the protected and unprotected groups

The toxic effect of cysteamine seems to counteract the protective effect when a relatively great number of daily irradiations and injections of cysteamine are given allowing no time for recovery either from irradiation or from toxicity

Discussion

Our investigation has demonstrated that cysteamine protects against such a long term effect of ionizing radiation as shortening of the life span It is however obvious that the magnitude of the protective effect is dependent on the AED and the time intervals between the exposure fractions At low AED s the radiation injury is not great enough to show a significant difference between the protected and unprotected animals although the tendency is clear At high AED s on the other hand the radiation injury in both groups is supralethal

The protective effect also differs with interval In some animals of the 160 R/3 days group the protective effect was astonishingly high The effect was significant at 160 R 7 days but at 160 R/1 day the effect was less marked although the tendency is obvious

It is not possible to draw any unequivocal conclusions from the results of the 80 R 1 day group It is necessary to give a great number of exposure fractions to

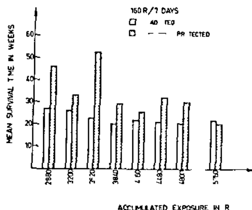


Fig 2 Mean survival time of mice irradiated with 160 R a week up to between 2 880 and 5 760 R

shows that there are a few long term survivors in the protected group, while all of the unprotected mice died within 8 weeks after the beginning of irradiation

The survival with time in per cent of survivors after the last irradiation is shown in Fig 7 Except in the lowest ALD group (1 600 R) and the highest groups (2 880 R, 3 200 R, and 3 520 R) there are some long term survivors in the protected group, which is not the case in the unprotected

4 *Fraction dose 160 R, interval 1 day* (Table 3 and Figs 8, 9, and 10) In this series also, the mean survival times for the protected groups are greater in the lowest ALD groups (480 R to 1 120 R) than in the unprotected and so are the median survival times in the two lowest exposure groups (Fig 8)

The mortality pattern at an ALD of 1 120 R (Fig 9) shows that in this case also a greater number of protected mice survived longer than unprotected animals

The survival after the last irradiation is presented in Fig 10 The difference in survival between the protected and unprotected is not as marked as in the 160 R/7 days and 160 R 3 days series, even though the tendency is clear

5 *Fraction dose 80 R interval 3 days* (Fig 11) The survival curves show a most interesting picture The mean survival times are of the same order of magnitude in both the protected and unprotected groups The slope of the curve in the protected group, however shows a higher mortality rate during the first half of the observation time During the latter half there are some long term survivors

The toxic effect of cysteamine seems to predominate over the radioprotective in the beginning Through selection of the more resistent animals or through acclimatization to the toxic agent the radioprotective action becomes evident on the long term survivors

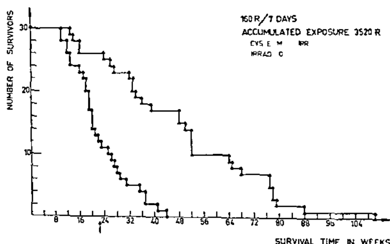


Fig 3 Mortality pattern in groups which had received 3 250 R Arrow indicates the last irradiation

6 *Fraction dose 80 R interval 1 day* (Table 4) The results in this series do not show any unequivocal differences in the means or the median life spans between the protected and unprotected groups

The toxic effect of cysteamine seems to counteract the protective effect when a relatively great number of daily irradiations and injections of cysteamine are given allowing no time for recovery either from irradiation or from toxicity

Discussion

Our investigation has demonstrated that cysteamine protects against such a long term effect of ionizing radiation as shortening of the life span It is however obvious that the magnitude of the protective effect is dependent on the AED and the time intervals between the exposure fractions At low AED s the radiation injury is not great enough to show a significant difference between the protected and unprotected animals although the tendency is clear At high AED s on the other hand the radiation injury in both groups is supralethal

The protective effect also differs with interval In some animals of the 160 R/3 days group the protective effect was astonishingly high The effect was significant at 160 R 7 days but at 160 R/1 day the effect was less marked although the tendency is obvious

It is not possible to draw any unequivocal conclusions from the results of the 80 R 1 day group It is necessary to give a great number of exposure fractions to

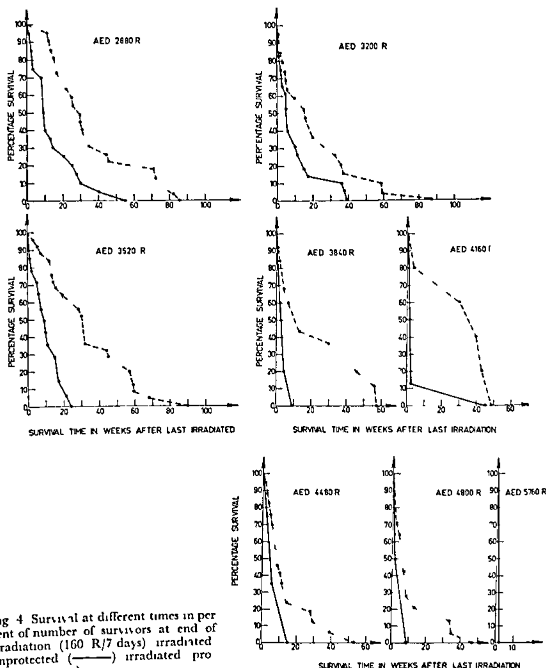


Fig 4 Survival at different times in per cent of number of survivors at end of irradiation (160 R/7 days) irradiated unprotected (———) irradiated protected (- -)

reach a lethal MED, which also means a great number of cysteamine injections It is possible that the intervals between the radiation fraction as well as between the injections of cysteamine are too short to allow enough recovery time from radiation and toxic injuries, which combined lead to a lethal accumulated dose of radiation and toxicity after a certain number of fractions In our earlier in

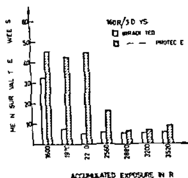


Fig 5 Mean survival time of mice irradiated with 160 R every 3 days up to between 1 600 and 3 520 R

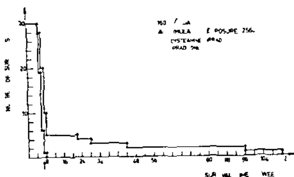
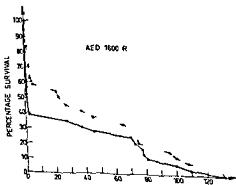
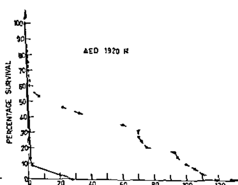
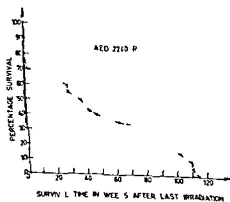


Fig 6 Mortality pattern in groups which had received 2 560 R Arrow indicates the last irradiation







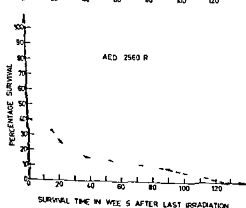


Fig 7 Survival at different times in per cent of number of survivors at end of irradiation (160 R/3 days) irradiated unprotected (———) and irradiated protected (- - -)

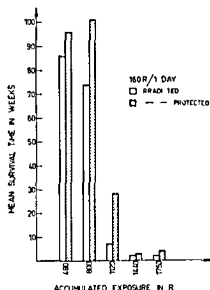


Fig 8 Mean survival time of mice irradiated with *160 R a day up to* between 480 and 1 760 R

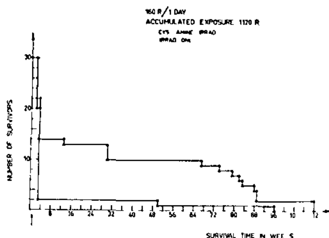


Fig 9 Mortality pattern in groups which had received *1 120 R* Arrow indicates the last irradiation

vestigation (NELSON et coll) it was seen that in some cases those animals which survived the irradiation period and the injections seemed to be protected against the acute effect, determined as LD 50 30 after the irradiation In the case of 160 R/1 day, the number of fractions necessary to reach the lethal accumulated dose of radiation are too few to attain the lethal accumulated dose for toxicity

Since the irradiation period in many of the series was extended over a relatively long time, in some cases up to more than half a year, there was no marked transition between the acute and the chronic mortality In some groups, however, all the animals survived the last irradiation, thus the mortality was due to the late effects alone

It was not possible to calculate a uniform dose reduction factor (DRF) since this factor seems to vary not only with the AFD but also with the length of the intervals between irradiations and the size of the fraction doses

There are relatively few published reports of investigations on the effects of chemical radioprotectors on the life span shortening effect of ionizing radiation

MAISIN et coll could not observe any influence of such protective agents, which yielded a better 30 day survival on the shortening of life span of rats surviving beyond the 30 days after irradiation with 600 R– 1 000 R The results of long term experiments are however always complicated by the common appearance of pulmonary affections

HOLLCROFT et coll, who irradiated S2H f He mice with a high single exposure of 900 R in anoxia found that cysteine under these conditions afforded a dose

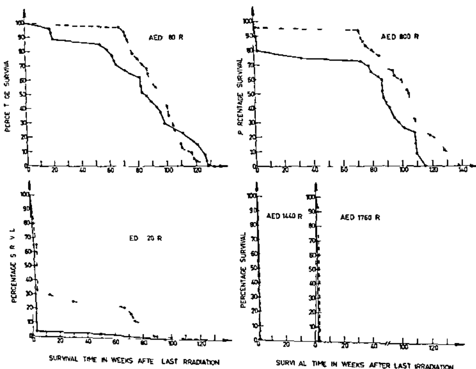


Fig. 10. Survival at different times in per cent of number of survivors at end of irradiation (160 R/1 day) irradiated unprotected (——) and irradiated protected (- - -)

reduction effect as measured by long term survival as well as in the acute phase.

UPTON et coll. gave RF mice MEG prior to irradiation with such low doses as 150 R and 300 R. They observed longer survival in the protected animals.

HOLLAENDER et coll. reported (1959) preliminary results of treatment with AET which show that the LD 50/30 days were nearly doubled. Comparable protection was also afforded against the life shortening action of radiation, the mean longevity of the 30-day survivors being more closely associated with the extent of the 30-day lethality than with the dose of radiation they received.

DOULL et coll. (1963) gave chemical protectors to female CF_1 mice prior to acute roentgen ray exposures of 400 R, 600 R and 800 R. The mortality was followed for a period of over 60 weeks. The percent mortality in each group was computed on the basis of the number of mice which were surviving at the end of the first 30-day period after irradiation.

Mice pretreated with PAPP, AET and MEA prior to 600 R and 800 R exhibited age corrected median survival times comparable with or less than those seen in animals given these roentgen doses without protection. All of these agents

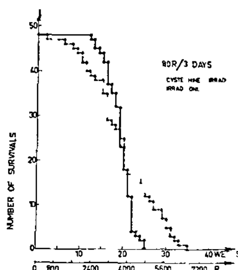


Fig 11 Mortality pattern in groups which had received 80 R every 3 days during life time

increased the median survival time of mice given 400 R but correction of the life *span shortening data for the increase in longevity produced by administration of* the agents alone eliminated the apparent protective effects in these animals The different groups are, however, not comparable without objections since some of the unprotected irradiated groups received the dose fractionated Furthermore, the untreated and unirradiated control group is relatively small

According to GROSGROVE et coll (1964), irradiation shortened the life span to an extent that varied with the dose (700 R to 1 400 R) but the degree of life shortening per roentgen decreased with increasing dose Although ALT had markedly protective effects against early lethality, its effects in protecting reduction of longevity in long term survivors was equivocal They used young adult female mice (101 × C3H) F_1 But they state that it is evident that AET protected against some but not all delayed somatic effects of whole body roentgen irradiation although in no cases did the protection appear to afford a factor of dose reduction approximating that obtained against the acutely lethal effect of the radiation (i e between 40 % and 50 %)

The results of HOLLCROFT et coll, UPTON et coll, HOLLAENDER et coll DOULL et coll, and COSGROVE et coll indicate the feasibility of protecting animals against delayed radiation injury as well as against acute lethality by measures which may be applied before irradiation

Our results are not contradictory to those of HOLLCROFT et coll UPTON et coll, HOLLAENDER et coll, DOULL et coll and COSGROVE et coll all of whom used single doses from 150 R to 900 R however whereas we gave sublethal fraction doses up to accumulated exposure doses in a wide range from sublethal to supralethal AED s

MEWISSEN (1957) however, gave total doses of 301 406 550 and 742 R divided in two fractions with an interval of 5 days to C57Bl mice He found that the cumulated survival curves of the animals still alive on the 60th day showed no significant difference between the mice protected with cysteamine and the control mice at total dose levels of 406 R and 550 R At 301 R and 742 R, however there was a questionable enhancement of survival in protected animals

DOULL et coll (1961) could not find any effect of cysteamine on the survival times of mice exposed to daily doses in the range of 40 R through 200 R In a later study by DOULL et coll (1961b), with daily doses of 70 90 and 125 R they confirmed their earlier results Cysteamine did not prevent the lethal effect of chronic exposure in the dosage range of 40 R through 200 R per day Rather pretreatment with cysteamine shortened the median life survival of chronically irradiated mice The effect was inversely related to the daily dose of radiation employed

The investigations of MEWISSEN and DOULL et coll were carried out in a way different from ours MEWISSEN used C57Bl mice which seem to show a rather high incidence of leukemia among the irradiated mice This is not the case with our CBA mice This may cause a bias in his survival curves DOULL found that pretreatment with cysteamine shortened the survival time of chronically irra diated mice In our 80 R 3 days series which is experimentally comparable we could not find any life shortening effect of cysteamine

In our cysteamine treated unirradiated control series a significant shortening of life span can be observed which of course is not only due to the toxic effects but also to the traumatic effect of the repeated intraperitoneal injections This effect was confirmed by the saline controls

NOBLE et coll (1960b) observed that male mice did not tolerate daily in traperitoneal administrations of AET at dosage levels greater than 100 mg kg/day without exhibiting cumulative toxic effects and mortality DOULL et coll (1961) found however that a daily administration of 200 mg kg could be tolerated by unirradiated mice for at least two months without the production of mortality or marked weight loss A daily administration of cysteamine seems to increase the tolerance Increasing levels of cysteamine to mice permits the animals to with stand a single administration of at least 400 mg kg This observation may explain the increased life span in some of the protected animals in the 80 R/3 day series

Among those investigators who have discussed a dose reduction factor the general opinion seems to be that if there is any DRF this is lower when calculated on the basis of late effects such as life span shortening than when based on acute effects From our investigations it is possible to draw the conclusion that cyste amine protects against such long term radiation sequelae as shortening of life

span When the AED is too low or too high, the protective effect is for obvious reasons not apparent The toxic effect of a great number of cysteamine injections in animals weakened by a great number of irradiations also complicates the picture in some series No uniform DRF can be calculated from our results The DRF seems to be dependent on the fraction dose, interval and AED

Acknowledgement

The authors are indebted to S *Jonsson* M *Hagstrom* S *Falk and* R *von Knorring for* their excellent technical assistance

SUMMARY

Groups of mice were exposed to repeated doses of 80 R and 160 R at various time intervals with a view to study the protective effect of cysteamine against late effects from sub lethal doses of irradiation The accumulated doses selected to fall definitely in the range between sub lethal and supra lethal doses Half the number of animals in each group were given cysteamine be fore each irradiation The conclusion may be drawn that in addition to the well known protec tive effect against acute injuries cysteamine also protects against such chronic effects as shortening of the life span

ZUSAMMENFASSUNG

Gruppen von Mausen wurden fraktionell mit Dosen von 80 R und 160 R bei verschiedenen Zeitintervallen bestrahlt um den Schutzeffekt von Cysteamin gegen die Spatwirkung von subletalen Dosen zu studieren Die Dosis Kumulation wurde so gewahlt dass sie sicher im Bereich von subletalen bis supraletalen Dosen liegt Die halbe Anzahl jeder Gruppe von Tieren erhielt Cysteamin vor jeder Bestrahlung Es konnte gezeigt werden dass Cysteamin ausser dem vorher bereits konstatierten Effekt mit Hinsicht auf akute Strahlenschaden auch gegen solche chronische Effekte wie Verkurzung der Lebensdauer eine Schutzwirkung besitzt

RÉSUMÉ

Pour étudier l effet protecteur de la cystéamine contre les effets tardifs de doses d irradiation subléthales les auteurs ont expose des groupes de souris a des doses répétées de 80 R et de 160 R a divers intervalles de temps Ils ont choisi les doses cumulatives de façon qu elles soient certainement comprises entre les limites des doses subléthales et supraléthales La moitie des animaux de chaque groupe a reçu de la cysteamine avant chaque irradiation Les résultats permettent de conclure que la cystéamine outre son effet protecteur bien connu contre les effets aigus des radiations confere aussi une protection contre un effet tel que le raccourcissement de la durée de vie

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COLLIMATORS AND COUNTING SYSTEMS FOR BRAIN SCANNING

by

C M E MATTHEWS

The ideal collimator would have both high efficiency and fine resolution but in practice a compromise between these two requirements must be reached Collimation is difficult with radioactive substances emitting high energy γ rays due to penetration through septa and side shielding This problem can be avoided by using radionuclides which only emit low energy γ rays, or positron emitters and coincidence counting In brain scanning this is particularly important because only a very small fraction of the total radioactivity in the body is present in the organ to be scanned Only these two groups of radio active substances will be considered in the present paper

In practice, the compromise reached between high efficiency and fine resolution is at present fixed rather arbitrarily In this paper the optimum compromise will be discussed theoretical considerations suggest that the resolution of typical collimators used for scanning may be too fine for the count rate which can be obtained

Various figures of merit have been used to compare collimators and counting systems (DEWEY & SINCLAIR 1961, BECK 1961, 1964 a, b MATTHEWS 1964

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1965) These are all based on statistical tests of significance of increased count rate over a suspected tumour area The use of such a statistical test implies that the optimum counting system is the one which enables the smallest tumours to be detected with a given statistical significance, and this is the assumption on which the present work is based Initially a uniform brain background radioactivity is assumed and later the effects of structure in the pattern of brain radioactivity will be considered Statistical significance for a uniform background is the first requirement for detection if the tumour cannot be detected with this assumption it will certainly not be detected if the effect of structures due for example to blood vessels, are taken into account

DEWEY & SINCLAIR (1961) used the following equation to test for statistical significance and BECK (1961) used a similar equation

$$n=\frac{\text{increase in count rate over target}}{\text{standard error of difference in count rate}}=\frac{R_T-R_{NT}}{\sqrt{\frac{R_T+R_{NT}}{t}}} \quad (1)$$

where R_T =count rate over target volume
R_{NT}=count rate over non target volume
t =time in which counts accumulate

If n is greater than about 3 the increase in count rate is statistically significant HAYBITTLE (1966) discussed the probability of observing a given standard deviation of difference in count rate for brain scans

Count rates in equation (1) may be expressed in terms of counting efficiencies for target and non target volumes and concentrations of radioactivity in these volumes

MATTHEWS (1965) using DEWEY & SINCLAIR s equation has shown that approximately

$$V_T \simeq \frac{k^1}{A\ B} \quad (2)$$

where V_T is the minimum target volume which can be detected with a given statistical significance A is a factor which depends on the biological and physical properties of the isotope used B is a factor which depends on the physical properties of the isotope in relation to the counting system (including the collimator) and k^1 is a constant for a given tumour and given time available for the scan (For large ratios of target to non target count rate there is a correction to this equation) MATTHEWS (1965) gives values of A for different radioactive substances

In this paper factor B will be considered (Camera systems will not be discussed although a similar treatment could be applied) B depends on the crys

tal, the collimator, and the attenuation in the source for the isotopes used and is given by the following equations (MATTHEWS 1965)

$$B = \sqrt{\frac{\eta\varepsilon_T \ a_T^2}{\varepsilon_{NT}\ a_{NT}}} \tag{3a}$$

or

$$B = \sqrt{\frac{\eta \ \varepsilon_T \ a_T}{\varepsilon_{NT}\ a_{NT}}} \text{ for coincidence counting} \tag{3b}$$

where η = crystal efficiency

ε_T = geometrical efficiency of collimator for target volume = ratio of number of photons striking crystal to number of photons emerging from source

ε_{NT} = same for non target volume

a_T = tissue attenuation factor due to absorption and scattering = number of photons from source reaching crystal ÷ number of photons reaching crystal if no absorption or scattering occurs

a_{NT} = same for non target volume

Thus, to detect the smallest tumours possible the collimator should be designed to give as large a value of B as possible, that is $\varepsilon_T/\varepsilon_{NT}$ should be as large as possible This may be used as a collimator figure of merit and depends only on the properties of the collimator In practice it is usually more convenient to take $\varepsilon_T^2\ a_T/\varepsilon_{NT}\ a_{NT}$ as the figure of merit

B can be measured experimentally with a phantom, or it can be calculated as will be shown

Design of collimators

BECK (1964 a, b) has discussed the design of collimators and has calculated a geometrical efficiency for a plane source He has pointed out that the design which gives maximum efficiency may not be ideal for other reasons If crystal diameter is much greater than the required resolution, or field of view then this field of view may vary rapidly with the distance from the focal point and the resolution diameter may be much greater at the end of the collimator than at the focal point BECK defines a shape factor K which is the ratio of the area of the field of view at the end of the collimator to the area of the field of view at the focal point For uniform resolution with depth K should be equal to one, but since this results in loss of efficiency there must be a compromise K may be fixed at the highest value which can be tolerated and efficiency can then be calculated Efficiency is therefore expressed in terms of K

The modification of BECK's procedure for design of collimators presented

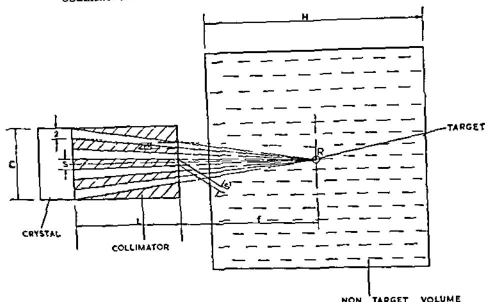


Fig 1 Relative positions of target and non target volumes and collimator For symbols used see text

here uses efficiency for a point source at the focus instead of for a plane source Since it is assumed that the optimum collimator is that which will enable the smallest tumour to be detected, it is desirable to make the efficiency for a small source as large as possible and as a first approximation a point source is considered BECK s plane source efficiency is then used to calculate the non target efficiency rather than the target efficiency It is assumed that either radionuclides emitting low energy γ rays are used with focusing collimators so that septum penetration is negligible or positron emitters with coincidence counting and cylindrical or conical single hole collimators

Focusing collimators for low energy γ rays The efficiency for a point source at the focus ε is given by the following equation

$$\varepsilon=\frac{Nr^2}{4(L+f)^2}=\frac{NRr^2}{4f^2(R+2r)^2} \qquad (4)$$

since $\frac{L}{f}=\frac{2r}{R}$

N = number of holes
r = radius of holes at crystal end of collimator
L = length of collimator
f = distance of focal point from end of collimator
R = radius of field of

Table 1

Values of parameters for a series of collimators

	N	r	L	C	τ	P	ϵ	$\frac{\epsilon_T^2}{\epsilon_{NT}} \frac{H}{I_{NT}}$	B
A Collimators with constant f, k and C $k=1.4$[illegible]	19	0.722	10.0	7.62	0.682	1.44	0.007[illegible]	0.00460	0.58
	37	0.501	5.30	7.62	0.642	1.89	0.0121	0.00423	0.55
	61	0.379	3.56	7.62	0.603	2.13	0.0144	0.0040[illegible]	0.54
	91	0.301	2.63	7.62	0.568	2.29	0.0157	0.00381	0.5[illegible]
B Collimators with constant f k and P $k=1.28$	19	1.14	9.21	11.8	0.710	2.47	0.0200	0.00418	0.55
	37	0.609	4.93	9.14	0.659	2.47	0.0186	0.00388	0.53
	61	0.409	3.31	8.16	0.615	2.47	0.0175	0.00366	0.51
	91	0.301	2.44	7.62	0.568	2.47	0.0161	0.00336	0.49

All dimensions in cm $f=10$ cm $s=0.1$ cm B calculated for ^{99m}Tc for $\eta=0.96$ $I_{NT}=$ [illegible]000 $\mu_0/(e^{\mu H}-1)=0.15$

The radius R is approximately equal to the 50% resolution diameter and will be taken as a measure of resolution

The positions of the collimator, crystal, and target and non target volumes are shown in Fig 1

Then

$$k=\frac{0.207\,C^2}{(R+2r)^2} \qquad \text{(Beck 1964 b)} \tag{5}$$

where k =shape factor =area of hexagonal field of view at end of collimator ÷area of circular field of view at focal point

C =crystal diameter

Also

$$\tau = \frac{4\,Nr^2}{C^2} \tag{6}$$

where τ =transmission ratio=fraction of crystal area exposed

$$\epsilon = 0.302\,\frac{\tau R^2 k}{f^2} \tag{7}$$

Hence, if collimators are designed in such a way as to keep k the shape factor equal to the largest value which can be tolerated then for a given focal length the efficiency is approximately proportional to R^2, and is independent of crystal diameter except in so far as this affects τ

Values of parameters for an example of a series of collimators designed in this way are given in Table 1

Efficiency can be calculated for given values of R f and k if τ is known τ depends on septum thickness ($=s$ at the crystal end of the collimator) hole radius (r) and diameter of crystal (C) It can be shown that

$$\tau = \frac{r^2}{C^2}\left(\frac{3\,(C+s)^2}{(2r+s)^2}+1\right) \simeq \frac{3}{\left(2+\frac{s}{r}\right)^2}+\frac{r^2}{C^2} \text{ for } C \gg s \tag{8}$$

The limit to τ will usually be the septum thickness as in practice it will be difficult to make this sufficiently thin The smallest septum thickness will be that at the outer end of the collimator s^1

Then

$$s = s^1\left(1+\frac{L}{f}\right) = s^1\left(1+\frac{2r}{R}\right) \tag{9}$$

$$\tau \simeq \frac{3}{\left(2+s^1\left(\frac{1}{r}+\frac{2}{R}\right)\right)^2}+\frac{r^2}{C^2} \tag{10}$$

This equation is required to calculate τ for a given value of s^1 the latter should of course be as small as possible to make τ as large as possible

To consider the effect of crystal diameter equation (5) is rearranged to give $C = 2\,2\,\sqrt{k}\,(R+2r)$ (11)

Hence if given values of k and R are required there is a minimum value for C the diameter of the crystal That is if the crystal diameter is too small compared with the required resolution then k and hence the efficiency will be reduced However if the crystal diameter is increased much above this minimum value there will be only a comparatively small gain in efficiency As the crystal diameter C is increased the length of the collimator must also be increased to keep k constant and so the solid angle is not greatly altered This is illustrated in Table 1 (B) As C increases the value of r increases for the same k and R i e the number of holes decreases Hence for a given septum thickness τ increases also Thus if k is to be kept constant the only advantage of using a larger crystal is that the fixed minimum septum thickness which can be constructed is smaller in relation to the crystal diameter so that τ is larger Thus the advantage to be gained by increasing crystal size much above the minimum value for a given resolution is comparatively small if constant re solution with depth is required HINE (1966) has also discussed this effect and demonstrated it experimentally

The efficiency calculated by means of equation (7) may be compared with the maximum efficiency which can be obtained if k is allowed to increase

$\frac{L}{f} = \sqrt{\frac{s}{R}}$ or $2r = \sqrt{Rs}$ (BECK also proves this for a sheet distribution)

$$\varepsilon_{max} = \frac{3\,R^2\,C^2}{64f^2\,(\sqrt{s}+\sqrt{R})^4} \tag{12}$$

and for this efficiency $h = \dfrac{0\,208\,C^2}{R\,(\sqrt{s}+\sqrt{R})^2}$ (13)

If maximum efficiency is required, regardless of h, then septum thickness is given by

$$s = s^1\left(1+\sqrt{\frac{s}{R}}\right) \tag{14}$$

$$= \frac{s^1}{2}\left(\left(2+\frac{s^1}{R}\right)+\sqrt{\left(2+\frac{s^1}{R}\right)^2-4}\right) \tag{15}$$

Procedure for design of collimators for low energy γ rays Let us assume that R, f, h and s^1 are specified Then one method of designing the optimum collimator would be to make r much greater than s, say $r=10s$ so as to make τ as large as possible Then from eq (9) the value of r would be given by

$$r \simeq \frac{10s^1\,R}{R-20s^1} \tag{16}$$

and C would be calculated from eq (11)

However this method tends to give too large a value of C, and so it is better to proceed as follows

(1) Specify C (depends on availability and cost)

(2) Find r from equation (11), then $L = \dfrac{2rf}{R}$

(3) Find s from equation (14)

(4) Find τ from equation (10)

(5) Find ε from equation (7)

ε and h may then be compared with ε_{max} (eq 12) and the value of h corresponding to ε_{max} from eq (13) In some cases it may be worth increasing the value of h a little (e g by increasing the number of holes) to gain a big increase in efficiency

The number of holes N is given by

$$N = \frac{3n^2+1}{4} \qquad n=1, 3, 5, 7$$

$$= \frac{3}{4}\left(\frac{C+s}{2r+s}\right)^2+\frac{1}{4}$$

It is usually necessary to alter the calculated value of r slightly to make n a whole number

Calculation of the B factor

For collimators designed as described above the value of B can be calculated approximately It is assumed that the target volume is small so that target efficiency is approximately the same as for a point source In practice of course efficiency will be lower than this but for a 1 cm diameter spherical target volume and a collimator with a radius of field of view of 2 cm for example, the difference will be not more than about 20 %

Then for a target source at the centre of the non target volume

$$\varepsilon_T \alpha_T = \varepsilon e^{-\mu H/2} \qquad (17)$$

where μ_a = total absorption coefficient
H = thickness of source

The use of the total absorption coefficient assumes that no γ rays scattered in the source reach the crystal In practice some of these scattered γ rays will give rise to counts and experiments indicate that this effect is more important for the non target volume than for the target volume but this is still being investigated Comparison between experimental and calculated values of B gives a measure of the contribution due to scattered γ rays Also the difference in calculated values when the true absorption coefficient is used gives the maximum possible effect of scatter (MATTHEWS 1965)

$\varepsilon_{NT} \alpha_{NT}$ can be calculated from BECK s equation for plane source efficiency in air by integrating with depth in tissue Let E be BECK s geometrical efficiency i e the efficiency for an extended plane source touching the end of the collimator Since as BECK states the efficiency for a plane source (in air) does not vary appreciably with distance this is also approximately the efficiency for a plane source at the focus

Then $E\sigma$ = number of photons passing through the collimator/sec
where σ = photons emitted/sec per unit area of the plane

For a volume source

$$\sigma = H^{\prime}\varrho = \frac{(1-e^{-\mu H})}{\mu_a}\varrho \qquad \text{(BECK 1961)}$$

where ϱ = photons emitted per unit volume of source
H = thickness of source
$H^{\prime}$ = equivalent thickness when attenuation is taken into account
μ_a = total absorption coefficient in volume source
number of photons passing through the collimator/sec

$$= F \frac{(1-e^{-\mu H})}{}$$

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Then $E\sigma$ = number of photons passing through the collimator/sec
where σ = photons emitted/sec per unit area of the plane

For a volume source

$$\sigma = H^1\varrho = \frac{(1-e^{-\mu H})}{\mu_0}\,\varrho \qquad \text{(BECK 1961)}$$

where ϱ = photons emitted per unit volume of source
H = thickness of source
H^1 = equivalent thickness when attenuation is taken into account
μ = total absorption coefficient in volume source
number of photons passing through the collimator/sec

$$= E\ \frac{(1-e^{-\mu H})}{}\ \rho$$

Total number of photons emitted by the source $=I_{xT}Q$

$$\varepsilon_{xT}\, a_{xT}=E\frac{(1-e^{-\mu H})}{\mu_0 I_{xT}} \tag{18}$$

Also

$$E=\frac{N\pi r^4 f^2}{4L^2(L+f)^2}=\frac{N\pi R^4 r}{16f\ (R+2r)} \qquad \text{(Beck 1964a)}$$

Combining this with eq (4) gives

$$\frac{\varepsilon}{E}=\frac{4}{\pi R}$$

$$\frac{\varepsilon_T\, a_T}{\varepsilon_{xT}\, a_{xT}}=\frac{4}{\pi R}\ \frac{\mu_0 e^{-\mu H/2}}{(1-e^{-\mu H})}\ V_{xT} \tag{19}$$

This equation is valid whether collimators are designed for maximum efficiency regardless of K, or for maximum efficiency for given K

Therefore for collimators designed for fixed K, from eqs (17) and (19)

$$B=\sqrt{\eta\frac{\varepsilon_T\ a_T}{\varepsilon_{xT}a_{xT}}}=\sqrt{\eta\ \frac{1.21\,K\pi}{\pi f}\ \frac{\mu_0}{(e^{\mu H}-1)}\ V_{xT}} \tag{20}$$

and for collimators designed for maximum efficiency

$$B=\sqrt{\eta\frac{\varepsilon_T\ a_T}{\varepsilon_{xT}a_{xT}}}=\sqrt{\eta\ \frac{3C}{16\pi f\ (\sqrt{R}+\sqrt{s})^4}\ \frac{\mu_0}{(e^{\mu H}-1)}\ I_{xT}} \tag{21}$$

Hence B can be calculated for given values of crystal efficiency

Similarly, for coincidence counting

$$\varepsilon_T a_T=\frac{C\ e^{-\mu H}}{16\ (L+f)} \tag{22}$$

$$\frac{\varepsilon_T a_T}{\varepsilon_{xT}a_{xT}}=\frac{4}{\pi R^2}\ \frac{V_{xT}}{H} \tag{23}$$

$$B=\sqrt{\eta^2\frac{\varepsilon_T{}^2 a_T{}^2}{\varepsilon_{xT}a_{xT}}}=\sqrt{\eta^2\ \frac{1}{\pi\,(L+f)^2}\ \frac{e^{-\mu H}}{H}\ I_{xT}} \tag{24}$$

since $R\simeq C/2$

In these equations L represents the length of the cylindrical single bore collimators and f is half the distance between the ends of these collimators

The collimator figure of merit mentioned on page 3 can now be found by making μ_0 tend to zero

For focusing collimators

$$\frac{\varepsilon_T}{\varepsilon_{xT}}=\frac{1.21K\pi}{\pi f}\ \frac{I_{xT}}{H}=\frac{4\varepsilon_T}{\pi R^2}\ \frac{I_{xT}}{H} \tag{25}$$

and for coincidence

$$\frac{\varepsilon_T^2}{\varepsilon_{NT}}=\frac{1}{\pi(L+f)^2}\,\frac{I_{NT}}{H}=\frac{k\varepsilon_T}{\pi R^2}\,\frac{I_{NT}}{H} \tag{26}$$

Both H and I_{NT} will be fixed for a given organ and in fact B does not depend on I_{NT} since it will cancel with the $\sqrt{I_{NT}}$ in the factor k^2 (see page 475). Hence it is more convenient to consider the quantity $\frac{\varepsilon_T^2}{\varepsilon_{NT}}\,\frac{H}{I_{NT}}$. Since τ does not vary greatly and f is determined by size of organ to be scanned, the value of this factor will depend mainly on k. Values of $\frac{\varepsilon_T^2}{\varepsilon_{NT}}\,\frac{H}{I_{NT}}$ are given in Table 1. This quantity varies little for given k and f for a wide range of collimators and crystal diameters. A value of 2.25 for k will give a ratio of radii of fields of view of 1.5 ($\sqrt{k}$) and this seems a reasonable compromise between high efficiency and uniform resolution with depth.

For coincidence counting the value of $\frac{\varepsilon_T^2}{\varepsilon_{NT}}\,\frac{H}{I_{NT}}$ will depend on how short the cylindrical collimator can be made and this will be determined by the random coincidence count rate. The value of both k and τ will always be 1 for coincidence. Thus the advantage for coincidence that the whole crystal is exposed is offset by the fact that efficiency cannot be increased by increasing k. In general it appears that focusing collimators will usually give a higher figure of merit than coincidence counting and this has been found in practice (MATTHEWS 1964). However if $L < < f$ for coincidence and $k=1$ for focusing collimators the values will be similar. Better results might be obtained with coincidence if focusing collimators were used as well as it would then be possible to use a larger crystal for a given resolution.

Considering now the value of B for different counting systems the crystal efficiency factor (η or η^2) and the factor due to absorption of γ rays in the source

$$\mu_0/(e^{\mu H}-1) \text{ or } e^{-\mu H}/H$$

must also be taken into account. Values for these factors are shown in Table 2 for a range of γ energies for two different crystal sizes. These are calculated for an organ 15 cm thick e.g. a head. As γ energy falls the μ_0 factor falls but the crystal efficiency rises so that optimum γ energy depends on crystal thickness. However high energy γ rays are unsuitable as already mentioned. For ^{125}I the energy is so low that the μ factor becomes very small due to increased photoelectric absorption. For coincidence counting the μ_0 factor is about the same as for low energy γ rays (excluding ^{125}I) but the crystal efficiency factor

Table 2

Effects of gamma energy on B factor

Isotope	γ energy (mainly) MeV	Crystal efficiency* η		$\frac{\mu}{e^{\mu H}-1}$	$\frac{\eta\mu}{e^{\mu H}-1}$		B**	
		1 $^1/_2$ diam 1 thick	3 diam 3 thick		1 $^1/_2$ × 1 crystal	3 × 3 crystal	1 $^1/_2$ × 1 crystal	3 × 3 crystal
^{1}I	0.511	0.21	0.45	0.028	0.0059	0.0126		
^{131}I	0.364	0.39	0.63	0.025	0.0098	0.0158		
^{203}Hg	0.280	0.59	0.72	0.021	0.0124	0.0151		
^{99m}Tc	0.140	0.92	0.96	0.015	0.0138	0.0144	0.60	0.61
^{197}Hg	0.077	0.98	1.0	0.013	0.0127	0.0130	0.58	0.58
^{125}I	0.035	1.0	1.0	0.003	0.0030	0.0030	0.28	0.28
				$\frac{e^{-\mu H}}{H}$	$\frac{\eta^2 e^{-\mu H}}{H}$			
^{1}I coincidence	0.511	0.20	*0.50*	*0.016*	*0.0032*	*0.0080*	*0.15*	*0.24*

* Source at 15 cm distance. For photoelectric peak only, except for coincidence where whole spectrum is included. Values of efficiencies from LAZAR (1958) for 3 × 3 crystal and from CROUTHAMEL (1960) and SIEGBAHN (1955) for 1 $^1/_2$ × 1 crystal.

** For V_{NT} = 5 000 ml, f = 10 cm, k = 2.25, τ = 0.60, and for coincidence L = 5 cm.

$\frac{\epsilon_{T^1}}{\epsilon_{NT}} \cdot \frac{H}{V_{NT}}$ = 0.0057 for focusing collimators and 0.0014 for coincidence (H = 15 cm).

is lower even though the whole spectrum is used instead of only the photoelectric peak. This disadvantage of coincidence counting could be overcome by using a very thick crystal.

Table 1 shows values of B for particular collimators for ^{99m}Tc. Table 2 also shows values of B for low energy γ rays calculated for a typical collimator.

The calculated values of B given in this paper are all for a point source at the focus, neglecting the effect of scattered γ rays which strike the crystal. The effect of scattering and the variation of B with depth in the non target volume is being investigated (P. M. KIBBY, to be published).

Minimum detectable tumour volume

The expected increase in count rate over a tumour may be calculated, using the following equations:

$$\left.\begin{aligned} R_T &= k\,C_T + (k^1 - k)\,C_{NT} \\ R_{NT} &= k^1\,C_{NT} \end{aligned}\right\} \text{DEWEY \& SINCLAIR (1961)}$$

where $C_T = \mu$Ci ml in tumour and C_{NT} in non target volume
k = cpm per μCi/ml in tumour and k^1 in non target volume

Also $k = \eta g \epsilon_T \rho_T I_T \times 2.22 \times 10^6$ }
and $k^1 = \eta g \epsilon_{NT} \rho_{NT} I_{NT} \times 2.22 \times 10^6$ } MATTHEWS (1965)

For example for 10 mCi ^{99m}Tc injected

$C_T \simeq 0.43$ μCi/ml and $C_{NT} = C_T/10 \simeq 0.043$ μCi/ml

assuming ^{99m}Tc is uniformly distributed in the extracellular space and that the tumour has 3 times more extracellular space per unit weight than the average for the whole body. Tumour/brain ratio is assumed to be 10 (MATTHEWS 1965, MATTHEWS & MALLARD 1965 and MATTHEWS & MOLINARO 1963)

Hence P_T and R_{NT} can be calculated using eqs (17) and (19) and the following values of the parameters

$g = 0.9$ $\eta = 0.96$ $H = 15$ cm $\epsilon = 0.012$ $R = 1.89$
$k = 6.95 \times 10^3 I_T$ and $k^1 = 3.7 \times 10^5$

For $I_T = 1$ that is a tumour of 1.24 cm diameter, $R_T = 15\,900$ cpm and $R_T - R_{NT} = 2\,700$ cpm

If $t = 0.0667$ min (see below) $n = 3.75$ and this tumour would be detected

If values of A and B are known eq (2) can also be used to calculate the diameter of the smallest tumour detectable with a given statistical significance. The constant k^1 in this equation is given by MATTHEWS (1965)

$$k^1 = \frac{\eta\sqrt{I_{NT}}}{126\sqrt{tq}} \tag{27}$$

where if $n > 3$ the increase in count rate is statistically significant
t = time in which counts accumulate (minutes)
q = (tumour extracellular space as ml/g of tumour)
− (whole body extracellular space as ml/g of body weight)

Also MATTHEWS 1965)

$$A = \sqrt{gDp\frac{(F-1)^2}{F}} \tag{28}$$

where g = number of photons emitted per disintegration
D = radioactivity given in mCi for a certain radiation dose to critical organs or whole body
F = (concentration of isotope in tumour) − (concentration of isotope in non target volume)
p = (concentration of isotope in tumour) − (concentration of isotope when uniformly distributed in e c f)

The $\sqrt{I_{NT}}$ factor in eq (25) will cancel out with the $\sqrt{I_{NT}}$ factor in the equation for B (eqs (3) and (21)). It is assumed that the non target volume extends

Table 2

Effects of gamma energy on B factor

Isotope	γ energy (mainly) MeV	Crystal efficiency* η		$\frac{\mu_0}{e^{\mu H}-1}$	$\frac{\eta\mu}{e^{\mu H}-1}$		B**	
		1 1/2 diam 1 thick	3 diam 3 thick		1 1/2 ×1 crystal	3 ×3 crystal	1 1/2 ×1 crystal	3 ×3 crystal
^{18}F	0 511	0 21	0 45	0 028	0 0059	0 0126		
^{131}I	0 364	0 39	0 63	0 025	0 0098	0 0158		
^{203}Hg	0 280	0 59	0 72	0 021	0 0124	0 0151		
^{99m}Tc	0 140	0 92	0 96	0 015	0 0138	0 0144	0 60	0 61
^{197}Hg	0 077	0 98	1 0	0 013	0 0127	0 0130	0 58	0 58
^{125}I	0 035	1 0	1 0	0 003	0 0030	0 0030	0 28	0 28
				$\frac{e^{-\mu H}}{H}$	$\frac{\eta^2 e^{-\mu H}}{H}$			
^{18}F coincidence	0 511	0 20	0 50	0 016	0 0032	0 0080	0 15	0 24

* Source at 15 cm distance For photoelectric peak only except for coincidence where whole spectrum is included Values of efficiencies from LAZAR (1958) for 3 ×3 crystal and from CROUTHAMEL (1960) and SIEGBAHN (1955) for 1 1/2 ×1 crystal

** For V_{NT}=5 000 ml f=10 cm k=2 25 τ=0 60 and for coincidence L=5 cm

$\frac{\varepsilon_T{}^2}{\varepsilon_{NT}} \frac{H}{V_{NT}}$=0 0052 for focusing collimators and 0 0014 for coincidence (H= 15 cm)

is lower even though the whole spectrum is used instead of only the photo electric peak This disadvantage of coincidence counting could be overcome by using a very thick crystal

Table 1 shows values of B for particular collimators for ^{99m}Tc Table 2 also shows values of B for low energy γ rays calculated for a typical collimator

The calculated values of B given in this paper are all for a point source at the focus, neglecting the effect of scattered γ rays which strike the crystal The effect of scattering and the variation of B with depth in the non target volume is being investigated (P M KIBBY, to be published)

Minimum detectable tumour volume

The expected increase in count rate over a tumour may be calculated, using the following equations

$$\left.\begin{aligned} R_T &= k\,C_T + (k^1 - k)C_{NT} \\ R_{NT} &= k^1 C_{NT} \end{aligned}\right\} \text{ DEWEY \& SINCLAIR (1961)}$$

Table 3

Minimum detectable tumour size

Isotope	mCi given*	t	B	Diameter of smallest tumour detected
F fluoroborate (coincidence)	8	12	0.15	1.58
			0.4	1.3
			0.50 (*maximum*)***	1.05
^{99m}Tc pertechnetate	44	19	0.50	0.91
			0.69 (*maximum*) *	0.82
	10	9	0.50	1.17
			0.69 (maximum)**	1.05
Hg neohydrin	0.36	1.6	0.30	2.47
			0.19 (maximum)	1.87

* for given radiation dose MATTHEWS (1965) and new data
** for $k = 3.76$
*** for $L = 0$, $\eta = 1$
for $\tau = 0.75$ $= 1$

tion to the resolution diameter of the collimator there will be a reduction in the maximum count rate over the tumour because of the averaging effect due to the movement of the collimator. The count rate increases to a maximum and falls again as the collimator is moved over the source as shown in Fig. 2. If counts are averaged over a distance d the maximum count rate will be reduced and a correction factor must be applied (MATTHEWS 1964). If d is large compared with the resolution diameter this correction factor will be important but if d is about equal to the 80 % resolution diameter the loss of count rate will be small. Hence the side of the square area over which dots are counted may be made equal to the 80 % resolution diameter. If the minimum size of tumour to be detected is known then d can be made equal to the 80 % diameter for the response curve for a source of that size instead of for a point source response curve. In the present calculations it will be assumed that $t = 4$ sec.

Table 3 shows values calculated from eq. (27) for diameter of smallest tumours detecable with $n = 3$ in the middle of a head for various isotopes and for different values of B. These are merely intended to indicate approximately the size of tumour which is detectable for given values of A and B if the assumptions made are correct. The maximum value of B shown is calculated for

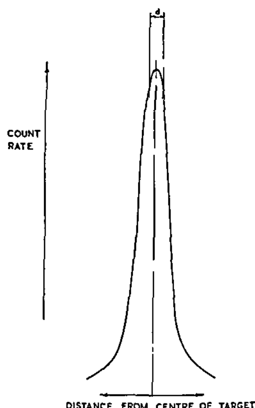


Fig 2 Variation in count rate as collimator moves over the target volume plotted against distance of collimator axis from centre of target d = distance over which counts should be averaged

beyond the field of view of the collimator, so that it is only the concentration of radioactivity in this volume which is important

Values of A for different isotopes are given by MATTHEWS (1965), q is assumed to be equal to 3 (MATTHEWS & MOLINARO 1963)

The time in which counts accumulate, t, is twice the ratemeter time constant for a photoscan However the photoscan is not used for quantitative statistical tests Using the dot scan, counts per unit area are determined in the region in which a tumour is suspected and in a region of background count rate Let the area in which counts per unit area are measured be a square of side d cm

Then

$$t=\frac{Td^2}{a}=\frac{d^2}{VS}$$

where T = total time available for scan

a = total area to be scanned

V = speed of scan

S = line separation

Therefore to make t large (so as to decrease k^2 and V_T) d must be large VS is fixed by the fixed values of T and a However, if d is made too large in rela

$$n = \frac{R_T - R_{NT}}{\sqrt{\dfrac{R_T + R_{NT} + \sigma_B^2}{t}}}$$

where σ_B = standard deviation of non target count rate due to variations in concentration of radioactivity.

The previous equation for t_T will now be multiplied by $\left(1 + \dfrac{\sigma_B^2}{2R_{NT}}\right)$. Thus σ_B^2/R_{NT} should be made as small as possible. The variation of σ_B with resolution could be calculated if the pattern of count rate corresponding to the true distribution of radioactivity was known. This could be found by carrying out a number of scans on normal subjects at a very low scanning speed so that statistical fluctuations were small. Although this would be tedious, once the pattern had been well established for a given isotope it would not have to be done again. The optimum value for the resolution could then be calculated.

Finally, the significance of these calculations must be emphasised. In some circumstances the minimum size of tumour which it is required to detect will be known, e.g. no symptoms may be produced until the tumour has reached a certain size so that patients are seldom examined with tumours smaller than this. If the value of n is already greater than 3 for this size of tumour there is no point in increasing it further and it would be better to improve resolution. However, it is more often the case that n is much less than 3 for some tumours which it is important to detect. In this case the efficiency must be increased as much as possible regardless of resolution, since there is no point in trying to obtain fine detail in a picture in which the object of interest cannot be distinguished. There may thus be a choice between optimum detection of small tumours and accurate localisation and outlining of larger tumours. In some cases it might be helpful to do a preliminary scan of the whole organ with a very coarse resolution, and then to use a finer collimator and a slower scan speed to examine in more detail the places which show a significant increase in count rate on the first scan.

Acknowledgement

I would like to thank Mr D. D. Vonberg for his support and encouragement.

SUMMARY

The design of collimators for low energy γ rays with uniform resolution with depth is discussed, and the effects of collimator efficiency and resolution on brain tumour detection is evaluated. It is estimated approximately that tumours in the middle of the head must be larger than 1.2 cm in diameter for detection using 10 mCi ^{99m}Tc. A method of calculating optimum collimator resolution is proposed.

$\eta=1$, $k=2\ 25$, $\tau=0\ 75$, $f=10$ V_{AT} is taken to be 5 000 ml but this does not affect the calculated tumour diameter Since many assumptions have been made in this calculation, the absolute values given are certainly not accurate, for example the effect of scattering will be to increase these minimum sizes However, the values shown do give an indication of the order of magnitude of the improvement which can be obtained with short lived isotopes (In practice ^{03}Hg is rather better for brain scanning than would appear from these figures owing to the lower radioactivity in blood and hence more uniform brain background than for extracellular substances like pertechnetate) Since with amounts of radioactivity commonly used it appears to be only possible to detect a tumour in the centre of the head if it is larger than about 1 2 cm in diameter, there is no point in using collimators with finer resolution than this

Optimum resolution

If collimators are designed for maximum efficiency regardless of shape factor, then target efficiency will increase with increasing resolution diameter, but not very rapidly, and B will be approximately inversely proportional to resolution On the other hand if collimators are designed for maximum efficiency for a given shape factor, then B is independent of resolution The reason for this is that as the resolution diameter decreases the target efficiency decreases, but the target/non target ratio increases and these two effects cancel out

However, n will still increase with increasing resolution diameter, since the larger the resolution diameter the larger can d be without a loss in count rate due to the averaging effect already discussed Thus smaller tumours can be detected if the resolution diameter is increased

Ideally, count rates from the whole organ should be measured with and without the tumour but this is of course not possible in practice In a symmetrical organ such as the head the count rates over the two halves of the organ can be compared, as in 'unbalance scans with ^{74}As (SWEET, MEALEY, BROWNELL & ARONOW 1959), or in point counting by PLANIOL's method (PLANIOL 1959) The extent to which the resolution diameter can be increased is limited for various reasons First it is necessary to measure non target count rate with negligible effect from the tumour Secondly there are variations in count rate over the normal head and the non target standard deviation will increase if resolution is too large Thirdly an increase in resolution diameter means an increase in minimum crystal diameter required for a given value of k and this will be limited by cost

The effect of variation of radioactivity concentration in normal brain might be allowed for by modifying the equation for n as follows

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CESIUM 137 BURDENS IN THE CANADIAN NORTH

by

V. K. MOHINDRA

Cesium 137 is one of the most important long-lived fallout products from nuclear weapon tests. Its presence in the human body was first reported by MILLER & MARINELLI (1956) and has since been the subject of considerable study both from the scientific and health points of view. Its concentration in the human body has in general remained well below the level considered significant from the health point of view. Recently, however, attention has been called to the exceptionally high levels found in the people living in certain northern regions — levels that appeared to approach the maximum levels recommended for continuous (life time) exposure.

LIDEN (1961) measured a number of Laplanders in a whole body counter and found substantially higher cesium 137 body burdens than in other Swedes. The average for Laplanders was about 300 nCi compared with about 8 nCi for the southern population. The higher levels were due to ingestion of reindeer meat in which it was found that the cesium 137 levels were about 280 times higher than in beef. The high concentration in the reindeer meat was attributed to the grazing habits of these animals. They feed on lichens and sedges and these plants are able to take up large amounts of fallout isotopes. Recently SVENSSON &

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ZUSAMMENFASSUNG

Gammastrahlen Kollimatoren mit gleichmassigem Tiefenauflosungsvermogen im niedrigen Energiebereich werden diskutiert und die Bedeutung ihrer Leistungsfahigkeit und ihr Auflosungsvermogen fur die Moglichkeit Gehirntumoren nachzuweisen wird ausgewertet Es lasst sich erschatzen dass Tumoren mitten im Kopf grosser als 1 2 cm im Diameter sein mussen um mit 10 mCi ^{99m}Tc entdeckt zu werden Eine Methode zur Berechnung des optimalen Auflosungsvermogens der Kollimatoren wird angegeben

RÉSUMÉ

L auteur étudie le dessin de collimateurs pour les rayons gamma de faible énergie donnant une résolution uniforme indépendante de la profondeur et examine les effets de l efficacité et de la résolution du collimateur sur la détection des tumeurs cérébrales Il estime que pour être détectée par 10 mCi de ^{99}Tc une tumeur située au milieu de la tete doit avoir un diamètre supérieur a 1,2 cm Il propose une méthode pour calculer la résolution optimale des collimateurs

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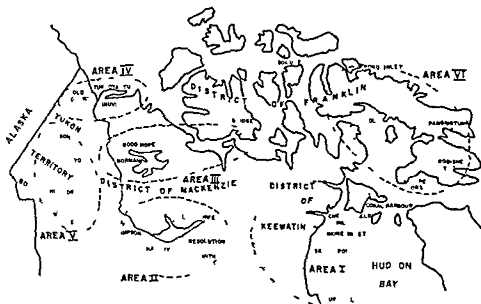


Fig 1 Sampling locations in the Canadian North

of the subjects The cesium 137 results were subsequently examined in relation to the following types of diet depending on the amount of caribou and reindeer meat eaten

Diet class A — Relatively large amounts of caribou and reindeer meat (consumption several times a week)

Diet class B — relatively small amounts of caribou and reindeer (consumption *occasionally* but on the average not more than once a week)

Diet class C — northern diet but no consumption of caribou or reindeer meat

Diet class D — urban diet in Ottawa Canada (included for comparison purposes)

Caribou and reindeer meat samples were also collected and analyzed for the cesium 137 content Samples were obtained with the help of the Area Administrators of the Department of Northern Affairs and National Resources Canadian Wildlife Services and the Inuvik Research Laboratory The samples were sun dried when possible or alternatively dried under infra red lamps before being sent to the Radiation Protection Division s laboratories for analysis. The results are presented in picocuries per pound of fresh meat

Most of the urine samples were nominally 24 hour specimens but when im

LIDEN (1965) have shown that lichens have an accumulation efficiency of about 100 per cent for cesium 137

MIETTINEN et coll (1964), in their studies of cesium 137 and potassium in Finnish Lapps and their diet, divided the subjects into various dietary groups They found that the cesium 137 body burden of reindeer breeder Lapps were comparatively much higher than in other dietary groups A maximum body burden of 790 nCi was recorded in a male reindeer breeder Lapp in 1961

Similar results were obtained in Alaska by other workers, e g HANSON et coll 1964) The mean cesium 137 body burden of villagers in Anaktuvuk Pass was about 450 nCi in 1962 and rose to 640 nCi in 1963 The comparatively high concentrations were found to result from eating caribou, an animal very similar to reindeer

Although lichens and sedges tend to accumulate high concentrations of other fallout isotopes, the main interest has been focused on cesium 137 because of its greater significance in relation to the human food chain This is because cesium 137 is deposited throughout the flesh of the animal and so is carried over into the human body when the meat is eaten In contrast, strontium 90 localizes in the animal bone and therefore does not contaminate the meat to the same extent

In view of these studies it was expected that the Canadian Eskimos who eat caribou meat would also show levels of cesium 137 and in 1963 a study was initiated by the Radiation Protection Division of the Department of National Health and Welfare to explore the situation This study is being carried out with the co-operation of the Department of Northern Affairs and National Resources Some preliminary data have already been reported (BIRD et coll 1965) The present report summarizes the results obtained in 1963, 1964, and 1965

Methods and Materials Since ^{137}Cs is a gamma emitter (0 66 MeV) internal contamination is most accurately determined by measuring the radiation emitted from the body in a 'whole body counter However, this technique requires the use of specialized, expensive equipment not available in the North at the time these measurements were performed The method was therefore not available for a rapid survey of the population group as a whole For this reason, initial estimates of the body burdens of the northern residents were made by analyzing urine samples Arrangements for the collection of urine samples from Eskimos were made with various nursing stations in the Canadian North and the Inuvik Research Laboratory The locations of the sampling stations are shown in Fig 1

Along with each sample, information was obtained about the dietary habits

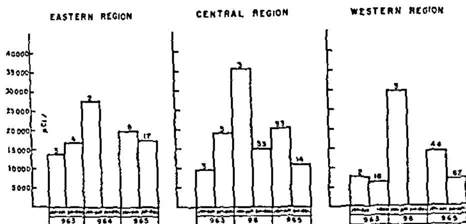


Fig 3 Half yearly average of cesium 137 levels in caribou and reindeer meat for eastern central and western regions (numbers on the histogram bars indicate the number of samples averaged)

Results

Cesium 137 levels in caribou and reindeer meat Average values of cesium 137 activity in caribou and reindeer meat samples obtained from the Canadian North are presented in Fig 2 It will be noted that there are two gaps in the data during some months no samples were available In addition some of the average values represented by histogram bars are based on a very small number of samples It seeems probable however that the cesium 137 concentration in the meat attained a maximum value between December 1963 and February 1964

In Fig 3 the same data are plotted but with the time interval increased from one month to six months In this way the average values are taken over a larger number of samples in each case and the effect of averaging over inadequate numbers is reduced The results are considered separately for eastern regions (areas I and VI) central regions (areas II and III) and western regions (areas IV and V) It is evident from the diagram that the eastern and central regions are at higher fallout levels than the western region

It may be noted that reindeer is available only in the western regions In 1963 there were only ten reindeer and eight caribou samples from this region The average cesium 137 activity was 5 533 pCi lb in reindeer meat and 7 400 pCi lb in caribou meat In 1965 there were 28 reindeer and 78 caribou samples and average activity was 9 827 pCi lb and 9 924 pCi lb respectively This suggests that there is no significant difference between the two animal species

Cesium 137 levels in Eskimo urine Average monthly values of cesium 137 concentration in urine samples are also shown in Fig 2 The same data is shown

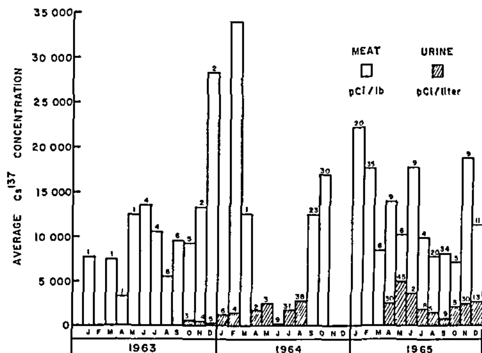


Fig 2 Monthly averages of cesium 137 levels in caribou and reindeer meat and in human urine (numbers on the histogram bars indicate the number of samples averaged)

possible to obtain full specimens the first voiding in the morning was taken In such cases, a daily passage of 1 400 ml was assumed in calculating the total amount of cesium 137 evacuated daily Since it was difficult to ensure that the 24 hour specimens included the complete daily passage of urine, attempts were made to correct the measured volume by reference to an assumed daily passage of creatinine or potassium but this attempt was later abandoned because it did not lead to any improvement in the accuracy of the data

In the laboratory, the cesium 137 content of urine samples and meat samples was measured by gamma spectrometric techniques using a 400 channel pulse height analyser and a 3″ × 3″ NaI (Tl) crystal The crystal detector assembly and sample were shielded by a 3″ thick lead ring castle which reduced the back ground activity for gamma radiation between 0 2 and 2 MeV by a factor of about 30 A correction was applied to take account of the contribution of scat tered gamma rays from the naturally occurring potassium 40 to the cesium 137 region of the spectrum

It should be pointed out that owing to the nomadic habits of Eskimos systematic urine sampling was not feasible In addition it was difficult to get reliable dietary information from the subjects supplying the specimens

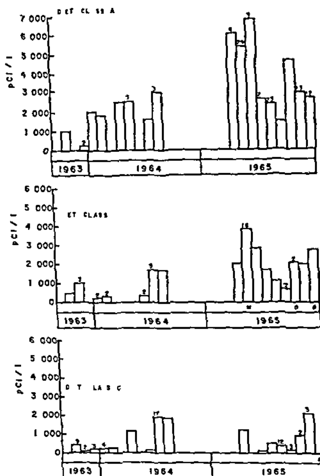


Fig 5 Effect of diet on cesium 137 levels in urine (numbers on the histogram bars indicate the number of samples averaged) Diet class A—relatively large amount of caribou and reindeer meat class B—relatively small amount of caribou and reindeer meat class C—northern diet but no consumption of caribou or reindeer meat

period) When the whole body is considered as the critical organ the ICRP tabulations show that the fraction of the amount of cesium 137 ingested which reaches the critical organ is unit ($f_w = 1.0$) and that the effective half life in the body is 70 days

The amount of cesium 137 eliminated via the urine was taken as 85 per cent of the total elimination (THREEFOOT et coll 1955) Therefore

$$E = \frac{U}{0.85} \tag{2}$$

where U is the amount of cesium 137 in microcuries in the full 24 hour urine sample

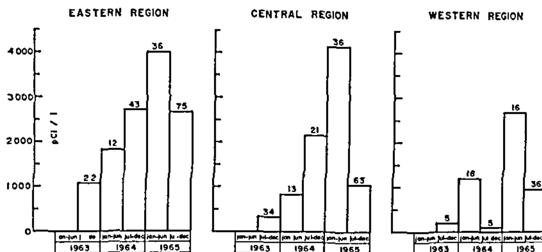


Fig 4 Half yearly averages of cesium 137 levels in human urine for eastern central and western regions (numbers on the histogram bars indicate the number of samples averaged)

replotted on a regional basis in Fig 4 Once again it is evident that the cesium 137 concentration in the urine samples is higher in the eastern and central regions and lower in the western region

The comparative levels for the three dietary groups are shown in Fig 5 The consumption of relatively large amounts of caribou and reindeer meat is reflected in correspondingly higher concentrations of cesium 137 in human urine A few of the individual results appear not to conform with this generalization but this may be due to the difficulty of obtaining reliable dietary information

Discussion

The amount of cesium 137 in the urine can be taken as a measure of the amount in the body However, in making estimates of body burdens on this basis it must be emphasized that precise evaluations cannot be expected There are many factors affecting the correlation which cannot be determined directly It is necessary therefore to introduce simplifying assumptions

Based on the biologic data and mathematical models used by the International Commission on Radiological Protection Report of Committee II (1959) the cesium 137 body burden of the subjects from whom the urine specimens were obtained was calculated by means of the expression

$$Q = E/\lambda \qquad (1)$$

The model assumes that there is a constant fraction, λ eliminated in unit time so that the amount, E, eliminated in unit time is directly proportional to the amount, Q, initially present in the body (at the beginning of the unit time

Conclusions and health significance

According to the ICRP Recommendations the maximum permissible body burden of ^{137}Cs that may be accumulated by any individual member of the general population is 3 μCi It is evident that the body burdens of the northern residents referred to in this study are generally well below the acceptable level The highest amount calculated was just sligthly higher

It should be noted that the maximum acceptable body burden implies a continuous life time exposure The cesium 137 concentrations are expected to decrease in the absence of further large scale nuclear testing There will therefore be no expectation of a significant effect on the health of the population and no necessity to consider restricting the normal consumption of caribou meat

Acknowledgements

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SUMMARY

Results of cesium 137 measurements in human urine and caribou meat samples from the Canadian North are presented for 1963 1964 and 1965 Estimates of body burdens were made from cesium 137 concentrations in urine specimens The average body burden of the people consuming relatively large quantities of caribou and reindeer meat were respectively 0 14 μCi 0 40 μCi and 0 56 μCi for those years The highest level observed corresponds to a body burden of 3 2 μCi It was comparatively higher in the eastern and central regions than in the western regions

ZUSAMMENFASSUNG

Die Resultate bei Messungen vom ^{137}Cs Gehalt im Menschen Urin und in Proben von Karibufleisch in den Jahren 1963 1964 und 1965 im Norden Kanadas werden vorgelegt Berechnungen der Ganskorper Aktivitat wurden aus der ^{137}Cs Konzentration im Urin vorgenommen Die durchschnittliche Aktivitat in Personen die verhaltnismassig grosse Quantitaten von Karibu und Renntier Fleisch konsumieren war 0 14 μCi 0 40 μCi und 0 56 μCi in diesen Jahren Der hochste observierte Wert entspricht eine Korper Aktivitat von 3 2 μCi Diese war verhaltnismassig hoher in den ostlichen und zentralen Regionen als in den westlichen Regionen

RÉSUMÉ

L auteur presente les resultats de mesures du cesium 137 dans l urine humaine et dans des échantillons de chair de caribou du Nord du Canada pour les annees 1963 1964 et 1965 L estimation de la charge corporelle a ete faite d après les concentrations en cesium 137 des

From eqs (1) and (2) we get

$$Q = 117.6\ U \text{ (microcuries)} \tag{3}$$

The estimates of the average body burdens of cesium 137 in μCi, for each diet class each year, are shown below

Type of diet	*1963*	*1964*	*1965*
A	0.14	0.40	0.56
B	0.13	0.20	0.35
C	0.05	0.08	0.10
D	0.03	0.03	0.02

The highest urinary level observed in 1965 was 19,500 pCi/litre which corresponds to a body burden of 3.2 μCi. By comparison the cesium 137 body burdens of a few Eskimos measured in the Division's whole body counter ranged from about 0.03 μCi to 1.05 μCi (Liss).

The assumptions in this calculation are subject to many uncertainties, the greatest being the value chosen for the effective half life in the body. This parameter has been measured by various workers (see UNSC Report Suppl. 14 (1965), p. 1393), who have reported values from 42 to 150 days, the mean being about 100 days. The value of 70 days (given in the ICRP tabulations) which was used in the present work, is close to the lower boundary of the range. It is possible therefore that the calculated body burdens shown in the table may be somewhat lower than the most probable value.

Examining the trend of the levels with time, it is evident that the concentrations in reindeer and caribou meat reached a maximum in the early months of 1964, whereas the concentrations in human urine peaked about a year later. A similar lag has been noted in Sweden. SVENSSON & LIDEN (1965) reported that concentrations of cesium 137 in Laplanders increased about 7 to 10 months after the increase was observed in the deposition on the lichen carpet. The length of the delay depends, of course, on the many factors involved in the food chain. For comparison it is interesting to note that there is a delay of about 5 months between the ^{137}Cs increase in the level in cow's milk and in the human body (MOHINDRA et coll. 1963).

The reason for the geographical variation noted earlier is not clear. It appears improbable that it could be due to variations in the total fallout deposited in each of the regions. The four fallout monitoring stations in the north, viz. Fort Churchill (eastern region), Yellowknife (central region), Inuvik and Whitehorse (western region) showed no appreciable difference in fallout levels in air and precipitation. It may be that the amount of cesium retained by different types of lichen is an important factor but this question has not been studied.

Conclusions and health significance

According to the ICRP Recommendations the maximum permissible body burden of ^{137}Cs that may be accumulated by any individual member of the general population is 3 μCi It is evident that the body burdens of the northern residents referred to in this study are generally well below the acceptable level The highest amount calculated was just slightly higher

It should be noted that the maximum acceptable body burden implies a continuous life time exposure The cesium 137 concentrations are expected to decrease in the absence of further large scale nuclear testing There will therefore be no expectation of a significant effect on the health of the population and no necessity to consider restricting the normal consumption of caribou meat

Acknowledgements

The author wishes to thank Dr A H Booth and Dr P M Bird for help and encouragement in the preparation of this article The analysis of the samples was carried out by Mr J H Gordon and Mrs Ardith A Downs

SUMMARY

Results of cesium 137 measurements in human urine and caribou meat samples from the Canadian North are presented for 1963 1964 and 1965 Estimates of body burdens were made from cesium 137 concentrations in urine specimens The average body burden of the people consuming relatively large quantities of caribou and reindeer meat were respectively 0 14 μCi 0 40 μCi and 0 56 μCi for those years The highest level observed corresponds to a body burden of 3 2 μCi It was comparatively higher in the eastern and central regions than in the western regions

ZUSAMMENFASSUNG

Die Resultate bei Messungen vom ^{137}Cs Gehalt im Menschen Urin und in Proben von Karibufleisch in den Jahren 1963 1964 und 1965 im Norden Kanadas werden vorgelegt Berechnungen der Ganskorper Aktivitat wurden aus der ^{137}Cs Konzentration im Urin vorgenommen Die durchschnittliche Aktivitat in Personen die verhaltnismassig grosse Quantitaten von Karibu und Renntier Fleisch konsumieren war 0 14 μCi 0 40 μCi und 0 56 μCi in diesen Jahren Der hochste observierte Wert entspricht eine Korper Aktivitat von 3 2 μCi Diese war verhaltnismassig hoher in den ostlichen und zentralen Regionen als in den westlichen Regionen

RÉSUMÉ

L auteur presente les resultats de mesures du cesium 137 dans l urine humaine et dans des echantillons de chair de caribou du Nord du Canada pour les annees 1963 1964 et 1965 L estimation de la charge corporelle a eté faite d apres les concentrations en cesium 137 des

echantillons d urine La charge corporelle moyenne des personnes qui consomment des quantites relativement grandes de viande de caribou et de renne ont ete respectivement de 0 14 μCi, 0 40 μCi et 0 56 μCi dans ces annees Les regions centrales et orientales ont des charges corporelles relativement plus elevees que les regions occidentales

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UNSC Report on the Effect of Atomic Radiation (1964) Suppl No 14

RADIUMHEMMET KAROLINSKA SJUKHUSET, UND INSTITUT FÜR RADIOPHYSIK
KAROLINSKA INSTITUTET STOCKHOLM SCHWEDEN

ELEKTRISCH GEHEIZTE KANÜLE ZUR INTRASELLAREN PARAFFININJEKTION NACH INTERSTITIELLER BESTRAHLUNG DER HYPOPHYSE

von

G. NOTTER, O. MELANDER und E. NORBERG

Die interstitielle Bestrahlung der Hypophyse durch Implantation von ^{90}Y, ^{198}Au und ^{32}P wird heute in vielen Kliniken als Alternative zur transcerebralen und transethmoidalen Hypophysektomie ausgeführt. Sie belastet den Patienten in geringerem Masse, ist schneller ausführbar und ist therapeutisch ebenso wirksam wie die meisten chirurgischen Hypophysektomien. Jedoch ist die Rate der Spätkomplikationen nach intensiver Bestrahlung der Hypophyse mit hohen Dosen grösser als nach chirurgischer Hypophysektomie.

Diese Komplikationen sind hauptsächlich zweierlei Art: (1) Strahlenschäden der Kranialnerven II—VI, (2) Liquorfisteln und sekundäre Meningitis.

Die erste Gruppe von Komplikationen kann durch eine sorgfältige Implantationstechnik vermieden werden, die am besten unter Durchleuchtungskontrolle mit Bildverstärkern in zwei zueinander senkrechten Ebenen erfolgt.

Liquorfisteln entstehen dagegen meistens nicht durch technische Fehler, sondern durch eine Strahlennekrose im Diaphragma sellae oder auf Grund einer anatomischen Anomalie, der sog. intrasellaren Duratasche, die mit der

Bei der Redaktion am 15. September 1966 eingegangen.



Abb. 1. Elektrisch geheizte Spezialkanüle zur Injektion von Paraffin

basalen Zisterne kommuniziert. Die Bindegewebsplatte des Diaphragma sellae trennt die Sella von der basalen Zisterne und liegt unmittelbar über der Hypophyse. Sie kann daher bei *einer Bestrahlung der Hypophysenperipherie* mit 70 000—100 000 rad, die für eine komplette Destruktion der Hypophyse benötigt werden (RASMUSSON 1953, NOTTER 1959), nicht ausreichend geschützt werden.

Liquorfisteln können sich spontan und komplikationslos schliessen, in vielen Fällen entwickelt sich jedoch früher oder später eine Meningitis. Zur Vermeidung dieser Komplikation schlugen FORREST & Mitarb. (1958) vor, den Bohrkanal in der vorderen Sellawand mit einer Metallschraube zu verschliessen, die mit einem Spezialinstrument durch die Nase eingeführt werden kann. Die Methode ist technisch relativ einfach und wurde auch von uns jahrelang angewandt. Sie verringert deutlich die Frequenz der Liquorfisteln, kann sie jedoch nicht ganz verhindern. Wir ziehen daher seit einem Jahre die von HAYEM & JURET (1962) vorgeschlagene intraselläre Injektion von Paraffin vor. Voraussetzung für eine sichere Wirkung ist jedoch eine exakte *intraselläre* Injektion von 0,25 bis 0,5 ml Paraffin, welche am zuverlässigsten unter

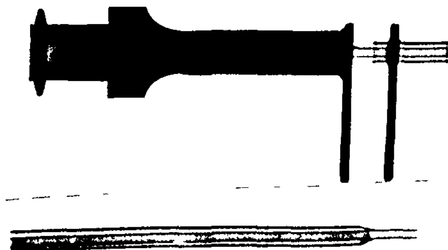


Abb. 2. Röntgenbild des elektrischen Anschlussteiles der Kanüle (oben) und der Kanülenspitze (unten)



Abb 3 Seitliches Rontgenbild der Sella unmittelbar nach Implantation von 4 Yttrium Metallzylindern in die Hypophyse (a) vierzehn Tage nach der Implantation partielle Auflosung der Metallzylinder) (b) und nach intrasellarer Injektion von Paraffin Goldpuder zur Behandlung einer Liquorfistel (c) Das Paraffin ist als dunner Belag auf der Vorderflache der Hypophyse und im Bohrkanal der Sellawand sichtbar

Durchleuchtungskontrolle geschieht Um das Paraffin im Rontgenbild sichtbar zu machen vermischen wir es mit Goldpulver oder mit Yttriumoxyd (Y_2O_3)

Die fur die Bestrahlung der Hypophyse benotigte Öffnung in der Sellavorderwand betragt 1 mm Beim Versuch flussiges Paraffin (Schmelzpunkt 42—44) durch eine 1 mm dicke Metallkanule in die Sella zu injizieren zeigte sich jedoch dass durch die hohe Warmeleitung der Metallkanule das Paraffin in ihr erstarrte bevor es injiziert werden konnte Dies war auch der Fall trotz maximaler Erwarmung der Kanule in kochendem Wasser oder in offener Flamme Wir sahen uns daher veranlasst eine elektrisch geheizte Kanule herzustellen die eine langsame und dosierbare Injektion von flussigem Paraffin moglich machte

Konstruktion und Heizeffekt der Kanule Das Rontgenbild der Kanule (Abb 2) zeigt zwei mit Glasfiber voneinander isolierte an einem Ende mit einem elektrischen Anschluss Stuck versehene und an der Spitze miteinander verlotete Kanulen aus rostfreiem Stahl (18/8) Die Diameter der ausseren Kanule sind 2 0/1 40 mm (Wanddicke 0 3 mm) die Diameter der inneren Kanule betragen 1 0 0 62 mm (Wanddicke 0 19 mm) Nur die Spitze der Kanule mit der dunnen Innenkanule wird partiell in die Sella eingefuhrt Der Widerstand der Kanule betragt 0 5 ohm und zusammen mit der von uns verwandten Anschlussleitung 1 2 ohm

Die Heizung der Kanule erfolgt mit einer Stromstarke von 1 A von einem Transformator mit einer Emk = 5 7 V und einem Widerstand von 2 4 ohm Wie das Diagramm zeigt erreicht die Kanule nach 5 Minuten eine konstante Temperatur von 55 die zur Verflussigung des Paraffines vollig ausreicht



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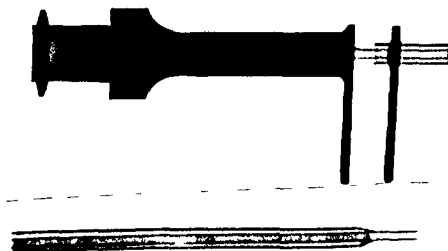


Abb. 2. Röntgenbild des elektrischen Anschlussteiles der Kanüle (oben) und der Kanülenspitze (unten)

ZUSAMMENFASSUNG

Eine neue elektrisch geheizte Spezialkanule zur Injektion von flussigem Paraffin Yttrium oxyd nach interstitieller Bestrahlung der Hypophyse wurde hergestellt Sie ermöglicht eine langsame und dosierte Injektion von flussigem Paraffin in die Sella unter Durchleuchtungs kontrolle Die Methode hat sich bei der Behandlung von Liquorfisteln und deren Prophylaxe bewahrt Schadliche Nebenwirkungen durch das intrasellar injizierte Paraffin wurden bisher nicht beobachtet

SUMMARY

A special electrically heated cannula has been designed for the injection of paraffin and yttrium oxide after interstitial pituitary irradiation The injection of liquid paraffin into the sella can be made slowly in fractionated amounts and under fluoroscopic control the method has been found particularly useful in preventing and dealing with cerebrospinal leakage No side effects from the intrasellularly injected paraffin have been noted

RÉSUMÉ

Les auteurs ont mis au point une nouvelle canule spéciale chauffée électriquement pour injecter de la paraffine liquide et de l oxyde d yttrium après irradiation interstitielle de l hypophyse Il permet une injection lente et dosée de paraffine liquide dans la selle sous controle radioscopique Cette méthode s est montrée utile pour le traitement et la prévention des fistules liquidiennes Jusqu à maintenant les auteurs n ont pas constaté d inconvénients dus à la paraffine injectée dans la selle

SCHRIFTTUM

BARRING N MELANDER O NOTTER G und WIDELL C Strontium 90 Applikator fur interstitielle Bestrahlung der Hypophyse Strahlentherapie (im Druck)

FORREST A BLAIR D and VALENTINE J Screw implantation of the pituitary with yttrium 90 Lancent 1958 II p 192

HAYEM M et JURET P Prophylaxie des fistules consécutives aux implantations d yttrium intrahypophysa re par mise en place d un écran paraffiné dans la selle turcique Presse Med 32 (1962) 1582

MULLAN S HARPER P TANI E et coll A nuclear needle for use in neurosurgery J Neurosurg 20 (1963) 940

NOTTER G A techn que for destruction of the hypophysis using Y^{90} spheres Acta radiol (1959) Suppl No 184

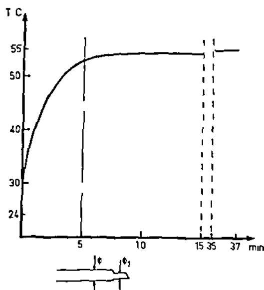


Abb 4 Erwarmung der Kanule bei Zimmer temperatur mit einem Strom von 1 A in Abhangigkeit zur Zeitdauer der Erwarmung

Die Kanule ist 265 mm lang (Abb 1) Die Variation des Kanulendiameters wahrend der Erhitzung ist ± 0,01 mm

Implantationstechnik Nach Fixation des Patienten im Riechert'schen stereotaktischen Gerat wird in intratrachealer Narkose die Fuhrungskanule mit einem ausseren Diameter von 2,8 mm entweder transnasal oder transethmoidal bis an die Vorderwand der Sella eingefuhrt Die Kanule wird fixiert und die Sellawand vorsichtig mit einem Bohrer perforiert Man spurt deutlich wenn der Bohrer in die Sella eindringt und die Hypophysenkapsel durchdringt Danach erfolgt die Implantation des radioaktiven Materials, oder nunmehr die interstitielle Bestrahlung mit einem ^{90}Sr-Applikator von 4,5 mm Lange und 1 mm Dicke (MULLAN & Mitarb 1963, BARRING & Mitarb 1966) Nach der Bestrahlung wird 0,25 bis 0,5 ml Paraffin Yttriumoxyd unter Durchleuchtungskontrolle in die Sella und die Bohrkanale in der Vorderwand injiziert Das flussige Paraffin erstarrt sofort im Gewebe und wird rontgenologisch als eine dunne Kontrastschicht zwischen Hypophyse und Sellawand sichtbar (Abb 3)

Behandlungsresultat

Seit dem 1 September 1965 wurden zwei Patienten mit einer langer bestehenden Liquorfistel erfolgreich mit Paraffininjektionen behandelt Bei weiteren zehn Patienten wurde Paraffin unmittelbar nach der Bestrahlung prophylaktisch injiziert In keinem dieser Falle kam es zu einer Fistelbildung Nachteilige Nebenerscheinungen von seiten des Paraffins wurden bisher nicht beobachtet

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Book review

RONTGEN UND KERNPHYSIK FUR MEDIZINER UND BIOPHYSIKER 2 Auflage Von R Glocker und E Macherauch 520 Seiten 375 Abbildungen und 156 Tabellen Georg Thieme Verlag Stuttgart 1965 Preis 69 DM

This is a completely revised and considerably enlarged edition of Professor Glocker s Rontgen und Radiumphysik fur Mediziner (1949) The first four chapters give a general review of radiation physics including roentgen tubes and machines while chapters 5 and 6 are devoted to the physical and chemical effects of radiation and to dosimetry Chapter 7 deals with protection in various types of radiation work Chapter 8 with roentgen diagnostics and therapy and Chapter 9 with medical and biological uses of radioisotopes Various topics are expounded in more detail in some addenda running in all to seventy pages and eight pages of an English—German technical dictionary are followed by author and subject indices

The physics parts of the book are more detailed than in most similar books written for radiologists but may sometimes be difficult to follow by those whose knowledge of physics is no more than that usually acquired in a medical education The contents are generally of a good standard although a number of inaccuracies and inadequate explanations have been noted a few numerical errors amount to several powers of ten

The most recent ICRU recommendations do not seem to have been considered in the text Some subjects have been rather briefly and inadequately covered e g radioisotope uses and photographic dosimetry It appears to the reviewer that German authors and firms not unnaturally perhaps have received somewhat more than a fair share of the space next followed by American authors while those from other countries are treated somewhat summarily

The book is nicely printed and illustrated There is however a drawback in that references in the book are made in relation to chapter and section or paragraph numbers and never to page numbers as these numbers do not appear on the page heads it is often difficult to find the page to which a certain reference relates

On the whole this is a good reference book and one that can be recommended to radiologists who have the necessary background in physics and to radiation physicists It should also be of some use to radiobiologists

Sten Benner